Medical Policy

Subject:	Deep Brain, Cortical, and Cerebellar Stimulation		
Document #:	SURG.00026	**Publish Date:**	09/27/2023
Status:	Reviewed	**Last Review Date:**	11/10/2022

Description/Scope

This document addresses the use of deep brain, cortical, and cerebellar stimulation. These technologies involve the use of electrical stimulation of a specific site on or within the brain via implanted unilateral or bilateral electrodes that are connected to a pulse generator. For deep brain stimulation (DBS) and cerebral stimulation, the generator may be implanted in the chest. For cortical stimulation, the generator may be implanted in the head. These forms of electrical stimulation are used in the treatment of intractable movement disorders characterized by involuntary tremors or muscle contractions as well as for seizure disorders.

Position Statement

Medically Necessary:

Unilateral or bilateral deep brain stimulation is considered **medically necessary** for individuals with disabling, medically unresponsive Parkinson's disease who meet the following criteria:

A. A minimal score of 30 points on the motor portion of the Unified Parkinson's Disease Rating Scale when the individual has been without medication for 12 hours; **and**
B. Either of the following:
    1. Motor complications of therapy that cannot be controlled pharmacologically; **or**
    2. Individuals with medically refractory tremor from Parkinson’s disease.

Unilateral or bilateral deep brain stimulation is considered **medically necessary** for individuals with medically refractory essential tremor.

Unilateral or bilateral deep brain stimulation of the subthalamic nucleus or globus pallidus is considered **medically necessary** for individuals with primary dystonia and who have **ALL** of the following:

A. Seven (7) years of age and older; **and**
B. Dystonia is chronic, refractory to drugs, and has a significant effect upon daily activity; **and**
C. Dystonia is not due to a secondary cause such as stroke, cerebral palsy, tumor, trauma, infection, multiple sclerosis, other neurodegenerative diseases, or medications; **and**
D. Dystonia manifests as one or more of the following:
    1. Cervical dystonia (torticollis); **or**
    2. Segmental dystonia; **or**
    3. Generalized dystonia; **or**
    4. Hemidystonia.

Unilateral or bilateral deep brain stimulation of the anterior nucleus of the thalamus is considered **medically necessary** for individuals with epilepsy and who have met **ALL** of the following criteria:

A. 18 years of age or older; **and**
B. Focal partial onset seizures with or without generalized seizure; **and**
C. Refractory to two or more antiepileptic medications; **and**
D. Currently having an average of three (3) or more disabling seizures (for example, motor partial seizures, complex partial seizures, or secondary generalized seizures) per month over the most recent three months; **and**
E. Absence of progressive neurological or medical conditions such as brain tumors or neurodegenerative disease; **and**
F. No history of non-epileptic seizures.

Bilateral deep brain stimulation of the striatal axis is considered **medically necessary** for individuals with obsessive compulsive disorder, when the following criteria have been met:

A. Age 18 years or older; **and**
B. Well documented obsessive compulsive disorder for 5 years or longer; **and**
C. Severe functional impairment as indicated by a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of 26 or greater despite conservative therapy meeting criteria 1 and 2 below**:**
    1. Cognitive-behavioral therapy with a minimum of 20 sessions involving personal (in-person or videoconference) interaction between the individual and a certified behavioral specialist; **and**
    2. Pharmacotherapy including both a and b below:
        a. A trial of clomipramine and at least two other serotonin-reuptake inhibitors at the maximum recommended dose or tolerated dose for at least 12 weeks; **and**
        b. Augmentation of at least one serotonin-reuptake inhibitor trial with first- or second-generation neuroleptic over a period of at least 1 month; **and**
D. Absence of all of the following:
    1. Contraindication to surgery including, but not limited to, any of the following:
        a. Significant neurological condition (for example, history of stroke, hypoxic brain injury, severe head trauma, cranial neoplasm, movement disorder); **or**
        b. Contraindication and/or inability to undergo MRI; **or**
        c. Clinically significant abnormality on MRI that may impair deep brain stimulator implantation; **or**
        d. Other medical contraindication; **and**
    2. Inability to adhere to close post-operative follow-up; **and**
    3. Inability to manage the device; **and**
    4. Current significant psychological condition (for example, psychosis, bipolar disorder, severe personality disorder) including, but not limited to, any of the following:
        a. Active substance use disorder within the past 6 months; **or**
        b. Manic episode in the preceding 3 years; **or**
        c. Psychotic disorder within the past 3 years; **or**
        d. Imminent risk of suicide.

The use of cortical stimulation is considered **medically necessary** for individuals with epilepsy who have met the criteria below:

A. 18 years of age or older; **and**
B. Partial onset seizures; **and**
C. Undergone diagnostic testing that localized no more than two (2) epileptogenic foci; **and**
D. Refractory to two or more antiepileptic medications; **and**

E. Currently having an average of three (3) or more disabling seizures (for example, motor partial seizures, complex partial seizures, or secondary generalized seizures) per month over the most recent three months.

Investigational and Not Medically Necessary:

Deep brain stimulation for tremor and dystonia from other causes such as trauma, multiple sclerosis (MS), degenerative disorders, metabolic disorders, infectious diseases, and drug-induced movement disorders is considered **investigational and not medically necessary.**

Deep brain stimulation is considered **investigational and not medically necessary** for all other conditions not identified above as medically necessary, including, but not limited to, the treatment of chronic cluster headache, and Tourette syndrome.

The use of cerebellar stimulation/pacing is considered **investigational and not medically necessary.**

The use of cortical stimulation is considered **investigational and not medically necessary** for all other indications, including but not limited to individuals who have not met the medically necessary criteria above.

Rationale

Deep Brain Stimulation for Dystonia, Parkinson's Disease, and Tremor

A variety of randomized studies have shown that deep brain stimulation (DBS) in various locations such as the globus pallidus, subthalamic nucleus or thalamus improved the symptoms of medically refractory Parkinson's disease compared either to sham stimulation or pallidotomy. Additionally, randomized controlled studies have shown that deep brain stimulation of the thalamus improves the symptoms of essential tremor compared to sham stimulation (Deuschl, 2000; Figuerias-Mendez, 2002; Merello, 1999; Obeso, 2001; Rehncrona, 2003; Schuepbach, 2013; Vitek, 2020). DBS has become a standard treatment for cases of Parkinson's disease when they become refractory to medical therapy. In the pivotal trial for DBS use in Parkinson's disease, the inclusion criteria were the presence of at least two cardinal features of parkinsonism (tremor, rigidity, and bradykinesia), a good response to levodopa, a minimal score of 30 points on the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) when the individual has been without medication for approximately 12 hours, and motor complications that could not be controlled with pharmacologic therapy (Obeso, 2001).

Primary (or idiopathic) dystonia is dystonia that is not due to a secondary cause such as stroke, cerebral palsy, tumor, trauma, infection, multiple sclerosis, medications, or a neurodegenerative disease. In 1997, the Activa® Dystonia Therapy System (Medtronic, Minneapolis, MN) received Pre-Market Approval (PMA) from the U.S. Food and Drug Administration (FDA) for unilateral thalamic stimulation for the suppression of tremor in the upper extremity in individuals who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability (Roper, 2016; Tan, 2016). In 2003, this system was granted a Humanitarian Devices Exemption (HDE) by the FDA for the treatment of primary dystonia. The FDA's decision was based on the results of deep brain stimulation in 201 individuals represented in 34 manuscripts. There were three studies that reported at least 10 cases of primary dystonia. In these studies, clinical improvement ranged from 50% to 88%. A total of 21 children were studied; 81% were older than 7 years. Among

these individuals there was about a 60% improvement in clinical scores. The FDA analysis of risk and probable benefit indicated that the only other treatment options for chronic refractory primary dystonia are neurodestructive procedures and DBS provides a reversible alternative.

The FDA Summary of Safety and Probable Benefit states:

> Limited treatment strategies exist for chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis). The three main approaches to the treatment of primary dystonia include systemic pharmacological agents (oral medications), local pharmacological agents (injected directly into affected muscles or their nerve supply), and destructive surgical or neurosurgical intervention. When local injection therapy is impractical or unsafe, and when systemic medications are not effective or produce unacceptable side effects, surgery may be considered. Surgical treatments of dystonia, including ablative therapies such as thalamotomies and pallidotomies, are irreversible, destructive procedures that can be associated with disabling complications. The patient group characterized in the Humanitarian Use Device application may also be candidates for deep brain stimulation therapy. Although there are a number of serious adverse events experienced by patients treated with deep brain stimulation, in the absence of therapy, chronic intractable dystonia can be very disabling and, in some cases, progress to a life threatening stage or constitute a major fixed handicap. When the age of dystonia occurs prior to the reaching their full adult size, the disease not only can affect normal psychosocial development (due to ostracization and/or prevention of normal peer relationships), but also cause irreparable damage to the skeletal system. As the body of the individual is contorted by the disease, the skeleton may be placed under constant severe stresses which may cause permanent disfigurement.
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> Risks associated with DBS therapy for dystonia appear to be similar to the risks associated with the performance of stereotactic surgery and the implantation of DBS systems for currently approved indications (Parkinson's Disease and Essential Tremor), except for when used in either child or adolescent patient groups. These additional risks include the use of general anesthetic instead of local anesthesia during implantation, potential lead strains or fractures related to elongation of the trunk of the patient (due to normal growth) while the length of implanted conductor (from the neurostimulator to the burr hole) remains fixed, the risk of lead migration due to patient head growth resulting in ineffective stimulation and the added risk of children being engaged in active play and sports activities that could damage components of the implanted system. The risks of lead strain, fracture and migration can be minimized by evaluating the patient's implanted lead/extension assembly for sufficient strain relief at regular post-implant follow-up sessions and by considering the replacement of the extension with one of greater length during other elective surgery procedures, such as during the regular change out of neurostimulators that must occur because of battery depletion. In cases where lead tip displacement may occur due to cranial growth the lead tip migration may be accommodated through reprogramming due to the number and spacing of the electrode contacts.
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> Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into accounts the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

Volkmann and colleagues (2012) published the results of a randomized controlled trial (RCT) involving 40 subjects with severe generalized or segmental idiopathic dystonia. Subjects were assigned to either sham or active neurostimulation of the internal globus pallidus. After implantation of the stimulation device in both groups, the experimental group received active treatment for 9 months. The control group had an initial 3-month period with their implanted device deactivated (sham treatment), followed by 6 months of active treatment. The initial intention of the study was to cease follow-up at the end of 9 months, but was extended to 5 years. Of the initial 40 subjects, 32 (80%) completed the 5-year study period. In an intention-to-treat analysis including all subjects, significant improvements were reported in dystonia severity at 3 years and 5 years compared with baseline (p=0.001 for both time periods). In the per-protocol population, results on the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) II motor score from 6 months to 3 years were statistically significant (p=0.001) and were sustained at the 5 year follow-up. A progressive improvement of dystonia severity beyond 6 months of neurostimulation was predominantly seen in subjects with generalized dystonia. Subjects with segmental dystonia demonstrated a relatively stable status from 6 months through 5 years. With the exception of speech and swallowing, all motor symptoms as well as the global clinical assessments of dystonia and pain showed significant improvements for up to 5 years. The responder analysis showed a beneficial response in 83% (30/36) of subjects at 6 months, 94% (29/31) at 3 years, and 81% (26/32) at 5 years. Use of antidystonic drugs gradually tapered off for most subjects, decreasing from 60% (20/40) at baseline to 35% (15/40) at 6 months. This improvement remained relatively constant, with 45% (14/31) of subjects on pharmacotherapy at 3 years and 8% (9/32) at 5 years. Dysarthria (n=16) and transient worsening of dystonia (n=7) were the most common non-serious adverse events. Twenty-one subjects experienced serious adverse events that required hospital admission. Sixteen of the 21 serious adverse events were device-related and were caused by technical defects, delayed infection, or migration. All serious adverse events in the original 9-month study phase and 66.6% of events during the long-term extension occurred in subjects with generalized dystonia. Fourteen of the 16 events of dysarthria occurred in subjects with segmental dystonia. This study demonstrates significant benefits of DBS in individuals with dystonia. However, substantial differences were found in outcomes between subjects with generalized vs. segmental dystonia. Further investigation into this issue is warranted.

Volkmann (2014) reported the results of a double-blind RCT involving 62 subjects with cervical dystonia assigned to receive either pallidal neurostimulation (n=32) or sham stimulation (n=30). Data were available for 60 subjects (97%) at 3 months and 56 subjects (90%) at 6 months. At 3 months, the reduction in dystonia severity as measured with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was significantly improved in the experimental group vs. controls (-5.1 points vs. 1.3; p=0.0024). Adverse events were reported in 11 experimental group subjects (21 events), with 5 events considered serious. The authors reported 11 serious adverse events (5 experimental group subjects vs. 6 controls), including infection, device explantation, and electrode dislocation. The results of this trial are promising and demonstrate a significant benefit to DBS therapy in individuals with cervical dystonia.

In 2018, the Congress of Neurological Surgeons (Rughani, 2018) published the following Level I recommendations on deep brain stimulation for the treatment of Parkinson's disease:

- Given that bilateral STN [subthalamic nucleus] DBS is at least as effective as bilateral GPi [globus pallidus internus] DBS in treating motor symptoms of Parkinson's disease (as measured by improvements in UPDRS-III [Unified Parkinson's Disease Rating Scale, part III] scores),

consideration can be given to the selection of either target in patients undergoing surgery to treat motor symptoms.
- There is insufficient evidence to make a generalizable recommendation regarding the target selection for reduction of dyskinesias. However, when the reduction of medication is not anticipated and there is a goal to reduce the severity of "on" medication dyskinesias, the GPi should be targeted.

On June 12, 2015, the FDA granted PMA approval for the Brio Neurostimulation system to reduce symptoms of Parkinson's disease and essential tremor in individuals with symptoms not adequately controlled with drug therapy. According to the FDA, data supporting the safety and effectiveness of the device included two clinical studies. The first included 136 subjects with Parkinson's disease followed for 3 months following device implantation. The second included 127 subjects with essential tremor followed for 6 months. Both studies demonstrated statistically significant improvement in the primary effectiveness endpoints when the device was turned on compared to when it was turned off.

Deep Brain Stimulation for Obsessive Compulsive Disorder

On February 19, 2009, the Reclaim™ device (Medtronic Neuro, Minneapolis, MN) received FDA approval under the HDE process. The FDA labeling states that the device is indicated for bilateral stimulation of the anterior limb of the internal capsule (AIC), as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant obsessive-compulsive disorder (OCD) in adults who have failed at least three selective serotonin reuptake inhibitors (SSRIs).

The use of DBS for OCD has been studied in multiple RCTs and case series studies, but the vast majority of them involved few subjects, which hampers the generalizability of their findings and does not provide a substantial picture of the safety hazards (Abelson, 2005; Barcia, 2019; Goodman, 2010; Greenberg, 2006, 2010; Holland, 2020; Huff, 2010; Huys, 2019; Jimenez, 2013; Nuttin, 1999; Polosan, 2019; Rauch, 2006; Roh, 2012; Tyagi, 2019; Voon, 2018; Winter, 2020). Only a small number of RCTs involve populations larger than 15 subjects.

As part of a clinical trial, Mallet and colleagues (2008) reported preliminary findings of a randomized, double-blind, crossover multicenter study of DBS of the subthalamic nucleus for treatment of refractory OCD. Included participants had received a primary diagnosis of OCD with a disease duration of more than 5 years, a score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) of more than 25 or one subscale score of more than 15, a score on the Global Assessment of Function (GAF) scale of less than 40, and severity of illness on the Clinical Global Impression (CGI) scale of more than 4. Participants were excluded if they were diagnosed with schizophrenic disorder, bipolar disorder, substance use disorder or dependence (except for dependence on nicotine), cluster A or B personality disorder, current severe major depressive episode, and a risk of suicide. Eighteen individuals were enrolled, 1 withdrew and 1 required removal of the stimulator before randomization because of infection. Of the 16 remaining subjects 14 received bilateral stimulation and the other 2 received unilateral stimulation. Three months after surgery, 8 individuals were randomly assigned to receive active stimulation for 3 months, followed by 1 month of washout, then 3 months of sham stimulation (on-off group). The other group followed the same treatment schedule in reverse (off-on group). New or worsening symptoms were classified as adverse events. It was recommended that medical treatment remain stable, and adjustments necessitated by the individual's psychiatric condition were recorded. Medication was held constant during the 10-month protocol, except for transient increase in

benzodiazepine therapy in 3 individuals and augmentation of neuroleptic treatment in 1 individual for exacerbated anxiety. The primary outcome measure was severity of OCD as assessed by the Y-BOCS measured at the end of each period. The Y-BOCS score was significantly lower at the end of active stimulation than at the end of the sham stimulation (mean score, 19 ± 8 vs. 28 ± 7; p=0.01) independent of the group and the period. No significant carryover effect between treatment phases was detected. Individuals who had active stimulation first (on-off group) tended to have a larger treatment effect than the off-on group (p=0.06). Outcomes on secondary measures of global health and functioning were significantly better at the end of the stimulation period. Scores on Montgomery and Åsberg Depression Scale (MADRS), Brief Scale for Anxiety, neuropsychological ratings, and self-reported disability (Sheehan Disability Scale) did not differ significantly at the end of treatment and sham sessions. Fifteen serious adverse events were reported in 11 individuals, the most serious a parenchymal brain hemorrhage. Transient motor and psychiatric symptoms induced by active stimulation resolved spontaneously or with adjustment of stimulation settings. Seven behavioral adverse events were reported in 5 individuals during stimulation. Hypomania was the main psychiatric serious adverse event; symptoms resolved with adjustment of stimulation settings. The authors note that the multicenter design might be a limitation of the study because of variation in targeting of stimulation. In addition, to preserve blinding, stimulation settings were kept below the threshold known to induce adverse effects and may have been too low to reduce symptoms. The authors concluded that these preliminary findings suggest that stimulation of the subthalamic nucleus may reduce the symptoms of severe forms of OCD, but it is associated with a substantial risk of serious adverse events.

Denys and colleagues (2010) published the results of an RCT involving 16 participants with OCD with a score greater than 28 on the Y-BOCS and failure of at least two SSRIs. Participants were excluded if they had clinically significant comorbid DSM-IV diagnoses such as schizophrenia, bipolar II disorder, alcohol or substance abuse in the preceding 6 months, and severe personality disorders. Other exclusion criteria included clinically significant and unstable neurologic or medical illnesses. Participants underwent bilateral implantation of a DBS device to the nucleus accumbens and then entered an open 8-month treatment phase, followed by a double-blind crossover phase with randomly assigned 2-week periods of active or sham stimulation, ending with an open 12-month maintenance phase. The authors reported that in the open phase, the mean Y-BOCS score decreased by 46%, from 33.7 (3.6) at baseline to 18.0 (11.4) after 8 months (p<0.001). Of the total 16 participants, 9 were noted to be responders, with a mean Y-BOCS score decrease of 23.7 (72%). In the double-blind, sham-controlled phase in which data for 14 participants was available, the mean Y-BOCS score difference between active and sham stimulation was 8.3 (25%; p=0.004). Depression and anxiety decreased significantly. Except for mild forgetfulness and word-finding problems, no permanent adverse events were reported.

Luyten and others (2016) described the results of a randomized, double-blind, crossover study of DBS of the anterior limbs of the internal capsule (ALIC) and bed nucleus of the stria terminalis (BST) in 24 subjects with OCD. Only 17 subjects completed the full trial. Individuals were excluded if they had a current or past psychotic disorder, any clinically significant disorder or medical illness affecting brain function or structure (other than motor tics or Gilles de la Tourette syndrome), or current or unstably remitted substance use disorder. Electrode placement was heterogeneous, with 5 subjects bilaterally in the BST, 1 unilaterally in the BST, 2 received stimulation on the BST in one hemisphere and the internal capsule (IC) in the contralateral side, 2 were stimulated bilaterally in the IC or the prereticular zone, 5 bilaterally in the ALIC, and 2 in both the BST and ALIC. Given the radius of the stimulation the investigators concluded that most subjects (82%) received stimulation in the BST, and/or IC (41%), or its anterior limb (35%). Multiple other areas adjacent to those areas may have received partial stimulation as well. Y-BOCS scores were significantly improved in the stimulation-on arm of the trial vs. the off arm (37%, p<0.017). Notably, 13

of the 17 crossover subjects also had significant Y-BOCS improvements in the off arm, indicating potential for placebo or microlesion effect. Similar results were found on the Hamilton Anxiety and Depression Rating Scales (HAM-A and HAM-D) and GAF scale, with 71%, 54%, and 15 point improvements, respectively ($p<0.001$ for all). No potential placebo effect was noted for the HAM results. Fourteen subjects had their stimulators turned on prematurely in the off arm due to "unbearable worsening of the symptoms", leading to a medial on duration of 89 days and median off duration of 44 days. In neuropsychological testing, significant improvements were noted on the Stroop test, Trail Making Test, and Auditory Verbal Learning test indicating improved executive functioning, mental processing and flexibility, and verbal learning and memory. However, no statistics were provided for these comparisons in the supplemental data. At 4 years follow-up, continuous improvement in Y-BOCS, HAM-A, HAM-D, and GAF scores were reported (66%, 58%, 67% and 30 points, respectively; $p<0.01$ for all). In an analysis of target vs. outcomes, the authors reported that stimulation of the BST was associated with significantly better outcomes when compared to ALIC stimulation ($p=0.01$). Multiple adverse events were reported throughout the trial, including skeletal fracture (n=6), seizures (n=5), suicide attempt (n=3), intracerebral hemorrhage (n=2), polytrauma (n=2), and obstructive sleep apnea (n=2). The authors concluded that DBS of the ALIC/BST area substantially alleviates symptoms of OCD in treatment refractory subjects. However, they further point out significant concern regarding the incidence of seizures in the study, emerging 2-5 years following initiation of stimulation of the BST, implicating this as a potential hazard.

In 2021, Mosley and colleagues published the results of a randomized, double-blind, sham-controlled trial investigating the effects of DBS at the bed nucleus of the stria terminalis in a sample of 9 Australian participants (mean age 47.9 ± 10.7 years) with severe, treatment-resistant OCD. After a 1-month postoperative recovery phase, participants entered a 3-month randomized phase during which their stimulators were either turned on or remained switched off. After this, participants entered a 12-month open-label stimulation phase incorporating a course of cognitive behavioral therapy (CBT). The primary outcome measure was OCD symptom severity as assessed by Y-BOCS score. In the blinded phase, there was a significant benefit of active stimulation over sham ($p=0.025$, mean difference 4.9 points). One participant developed an acute implantation effect assessed by a reduction in the intensity of obsessive thoughts for 72 hours post-operatively before returning to baseline. One participant did not reach the target amplitude of 4.5 Volts during the blinded phase due to mild agitation at higher amplitudes, but due to a robust observed symptom reduction, a lower amplitude was selected for chronic stimulation. One participant showed a placebo response to sham stimulation with a 20% reduction in Y-BOCS. After the open phase, the mean reduction in Y-BOCS was 17.4 ± 2.0 points ($\chi 2$ (11) = 39.9, $p=3.7 \times 10\text{-}5$), with 7 participants classified as responders. The addition of CBT resulted in a further Y-BOCS reduction of 4.8 ± 3.9 points ($p=0.011$). There were nine serious adverse events. One participant had medication adjustments due to non-response to DBS and persistence of clinically significant symptoms. It is noted that this participant was in the stimulation group during the blinded phase of the trial. The participant's response resulted in five of the serious adverse events due to hospitalization for symptom management. Another participant was readmitted to the hospital on two occasions to manage recurrence of depressive symptoms. One participant developed an infection during the open-label phase necessitating DBS device explantation and exit from the trial. Another device related serious adverse event required re-siting of a DBS electrode that migrated from target implantation. All participants required replacement of the implantable generator due to battery depletion during the study. The authors noted the small sample size as a limitation of the trial, though it is consistent with other clinical trials of DBS for treatment-resistant psychiatric indications. The study is also limited by the short duration of its blinded phase and lack of long-term follow-up.

Greenberg and colleagues (2010) published the results of a multi-center study involving DBS implantation into the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS) in 26 subjects with severe treatment-resistant OCD. Subjects had a score of greater than or equal to 28 on the Y-BOCS, had failed a minimum of two trials with SSRIs, and had symptoms for a minimum of 5 years. Some of the exclusionary criteria included if there was a history of a current or past psychotic disorder, a manic episode within the preceding 3 years, current or unstably remitted substance use disorder or dependence, a clinical history of severe personality disorder, if there was an imminent risk of suicide, any clinically significant abnormality on MRI, any contraindication or inability to undergo MRI, and any current clinically significant neurological disorder or medical illness except for tic disorders. At the final 36 months post-implant time point, mean Y-BOCS reached 20.9 ± 2.4, down from 34.0 ± 0.5 (p=0.002), and the number of subjects meeting criteria for full response (decrease in Y-BOCS ≥ 35) was 61.5% (16/26). A total of 73% of subjects had at least a 25% decrease in Y-BOCS. The GAF score was available for 21 participants and rose from a mean of 34.8 ± 1.1 at baseline to 59.05 ± 3.3 at 36 months (p=0.006). Serious adverse events included intracerebral hemorrhage in 2 subjects (7.7%) following lead insertion, and both cases resolved spontaneously. Another subject (3.8%) developed generalized tonic-clonic seizures following implantation, necessitating treatment with phenytoin for 1 month postoperatively. Seizures did not recur following cessation of medical therapy. Finally, 1 subject (3.8%) developed a superficial wound infection which resolved successfully with medical treatment. Lead replacement was required in 2 (7.7%) subjects due to breakage. Therapy-related complications included 4 cases of increased depression or suicidal ideation in 3 subjects (11.5%), increased severity of OCD was reported in 3 subjects (11.5%), hypomania in 1 subject (3.8%), and domestic problems/irritability associated with stimulation were reported in 1 subject (3.8%). The authors concluded that their results suggest that neural networks relevant to therapeutic improvement might be modulated more effectively at a more posterior target.

In 2015, Alonso and others conducted a meta-analysis of studies addressing the use of DBS for the treatment of OCD. They included 31 studies involving 116 subjects in the analysis. The studies mentioned above (Denys, 2010; Greenberg, 2010; Mallet, 2008) were included, and represented 50% of the subject population. The remaining 28 studies accounted for the rest of the subject pool, representing a mean of 2.07 subjects per study (range=1-10). Implantation in striatal areas, anterior limb of the internal capsule, ventral capsule and ventral striatum, nucleus accumbens and ventral caudate was reported in 83 subjects. Implantation in the subthalamic nucleus was reported in 27 subjects, and implantation in the inferior thalamic peduncle was reported in 6 subjects. Global percentage of Y-BOCS reduction was estimated at 45.1% and global percentage of responders at 60.0%. The authors reported that better response was associated with older age at OCD onset and presence of sexual/religious obsessions and compulsions. No significant differences were detected in efficacy between targets. There were only 5 dropouts reported, and adverse effects were generally reported as mild, transient, and reversible. The authors concluded that their analysis confirms that DBS constitutes a valid alternative to lesional surgery for individuals with severe, therapy-refractory OCD. However, they noted that well-controlled, randomized studies with larger samples are needed to establish the optimal targeting and stimulation conditions and to extend the analysis of clinical predictors of outcome.

In 2021, Hageman and colleagues published a meta-analysis comparing the clinical outcomes of individuals who underwent ablative surgery or DBS. The investigators focused on the efficacy of reducing symptoms, reported adverse events, the effect on depression and anxiety, and the effect on global functioning. Random effects meta-analyses were performed on 38 articles focusing on the efficacy in reducing OCD symptoms as measured by a reduction in the Y-BOCS score and the responder rate (≥ 35% reduction in Y-BOCS score). Responder rates were 48% and 53% after 12 to 16 months and 56% and 57% at last follow-up for ablative surgery and DBS, respectively.

The effect sizes in the reduction of Y-BOCS scores were considered very large in both ablative surgery and DBS indicating that they both result in clinically relevant improvements in individuals with treatment-refractory OCD. Regarding these outcomes, meta-regression showed no statistically significant difference between ablative surgery and DBS. Regarding adverse events, meta-regression showed that the difference in occurrence of impulsivity, agitation, and disinhibition between ablative surgery and DBS studies was statistically significant with the rate per patient year being higher for DBS (p=0.024). There was also a trend toward statistically significant (p=0.055) more cases of mania or hypomania in DBS. However, in most cases, these adverse events disappeared spontaneously after a few days or could be managed with adjustment to DBS settings. The authors noted that while healthcare practitioners may be more inclined towards utilization of DBS due to its reversibility, choice of intervention should carefully assess factors such as the risk of developing impulsivity. Some limitations included high heterogeneity between studies, anatomical target differences, differences in stimulation parameters for DBS, lack of control conditions, and a lack of adverse event reporting in many studies.

In 2014, Kohl and colleagues published a systematic review comparing and evaluating the effectiveness of different targeted brain structures for the treatment of OCD. The investigators identified 25 studies including 109 participants reporting on 5 different DBS target structures: the ALIC (n=14), nucleus accumbens (n=37), ventral capsule/ventral striatum (n=29), subthalamic nucleus (n=23), and inferior thalamic peduncle (n=6). The studies included were primarily case reports or case series and all included information on the Y-BOCS as an assessment tool. The follow-up period for most studies was less than 36 months with 11 studies reporting follow-up of 1 year or less. The response rates for the ALIC (75%), nucleus accumbens (45.5%), ventral capsule/ventral striatum (50%), and subthalamic nucleus (57.1%) were similar while the results for the inferior thalamic peduncle was higher (100%). However, the authors caution interpreting that as superiority as the number of cases was low. Serious adverse events included two seizures and three intracerebral hemorrhages. Stimulation related side effects were transient and declined after adjusting parameters. Device related adverse events included breaks in stimulating leads and battery failure, which the authors note could precede unfavorable changes in mood and behavior. Some study limitations included study design and methodology, lack of comparator, and sample size.

In a systematic review, Naesström and colleagues (2016) reviewed available evidence on multiple psychiatric indications for DBS with a focus on therapy-refractory OCD and major depressive disorder. A total of 52 studies met their inclusion criteria describing a total of 286 unique individuals treated with DBS for psychiatric indications. The sample included 18 studies that described 112 individuals treated with DBS for OCD in 6 different anatomical targets, while 9 studies included 100 individuals treated with DBS for major depressive disorder in 5 different targets. Regarding OCD, the studies did not differ substantially regarding inclusion criteria. Participant criteria mostly included: those with severe OCD, defined by a minimum Y-BOCS score of 25 to 28, for at least 5 years; therapy-refractory symptoms after three attempts using SSRIs including clomipramine; additive therapy with a neuroleptic and/or a benzodiazepine; and attendance to a minimum of 16-20 CBT sessions. Regarding the use of DBS in depression, the follow-up intervals and tools for evaluation varied which complicated the comparison. Though many of the included studies demonstrated improvements in OCD, they are limited by their design, lack of randomized controlled data, differing tools for evaluation, and varied definitions of response and remission. Furthermore, there was a lack of consensus on optimal targets for DBS and over half of the studies on its use in OCD included 4 participants or less.

Menchón and colleagues (2021) published the results of a case series study involving 30 subjects with severe to extreme treatment-refractory OCD treated with bilateral DBS of the ALIC. Subjects were followed for 12 months.

Mean Y-BOCS scores decreased significantly from baseline to 12 months (34.9 vs. 20.2, no p-value provided). At 12 months, the number of subjects deemed responders (at least a 35% decrease in Y-BOCS) was 60% (n=18). All subjects were reported to have experienced adverse events, with a total of 195 events, including non-specified neurological disorders (n=10), headaches (n=11), anxiety disorders (n=8), sleep disorders/disturbance (n=9), and infections (n=9). The majority were determined to be mild or moderate (89.74%) and 63% were determined to have been device-related. A total of 36 serious adverse events occurred, including worsening OCD (n=9), seizures (n=4), anxiety (n=2) and hypomania (n=2). Adverse events led to temporary cessation of treatment in 8 subjects. The majority of events were resolved by the end of testing, but 5% (9 events in 7 subjects) were ongoing, including hypothyroidism, worsening emotional instability, dizziness, hypercholesterolemia, gastritis, and implant site pain. A total of 588 acute stimulation-induced effects were reported during visits at which stimulation parameters were adjusted, including hot/cold sensation, mood and anxiety effects, and skin flushing.

Denys (2020) reported the results of a case series study involving 70 subjects with refractory OCD treated with bilateral DBS of the ventral ALIC (vALIC). Of these, 16 subjects had participated in this group's previously reported study. In this study, absolute contraindications for DBS were the presence of psychotic disorders, substance use disorder within the past 3 months, and unstable neurological or coagulation disorders. In contrast to their initial study (Denys, 2010), severe comorbid DSM diagnoses such as bipolar disorder, autism, or personality disorder, were instead relative contraindications that relied on the input of a multidisciplinary team to determine appropriateness of treatment with DBS. Concomitant CBT was provided to 57 subjects to decrease compulsive behavior and avoidance, and to test DBS setting. The remaining 13 subjects did not receive CBT on the basis of good response to DBS alone. At 12 months of active stimulation demonstrated a mean decrease of Y-BOCS scores of 13.5 points (34 at baseline to 20.5, $p<0.0001$). Overall, 62% (n=36) of subjects were reported as responders with a mean Y-BOCS decrease of 20.9 points. Another 17% (n=17%) were determined to be partial responders with mean Y-BOCS decrease of 99 points. There were a total of 22 non-responders (31%) with mean Y-BOCS of 3.3 points. At 12 months HAM-D scores decreased from 21 to 9.8 ($p<0.001$). Explantation occurred in 2 subjects due to infection and these subjects underwent subsequent reimplantation within 3 months. Another 6 subjects underwent electrode reimplantation or retraction due to poor rooting in the vALIC (n=4), they were implanted too deeply (n=1), or migration (n=1). The number of overall adverse events was not reported. However, stimulation-related adverse events included hypomania (39%), impulsivity (19%), and sleeping disorders (46%). Other adverse events reported included headache (36%), pain around burr holes (17%), pulling of the extension leads (30%), and scalp paresthesia (20%). The authors noted that temporary cessation of stimulation led to severe depression and severe anxiety. Suicide attempts were reported for 3 subjects, only 1 of which was considered stimulation-related. The authors concluded that their findings provided evidence of significant benefit of DBS of the vALIC for treatment resistant OCD. However, the commented that "future sham-controlled trials should be conducted to provide further evidence that the effects of DBS for OCD extend beyond placebo effect."

Garnaat (2014) reported a study assessing the size of the population of potential subjects who may qualify for DBS for OCD. Using baseline data from the Brown Longitudinal Obsessive-Compulsive Study (BLOCS), which involved data from 325 treatment seeking subjects, the authors used the inclusion and exclusion criteria from a study of DBS for OCD (ClinicalTrials.gov Identifier: NCT00640133) to determine how many BLOCS subjects would have qualified for DBS. Using a Y-BOCS minimum threshold of 28, they reported that only 19% of subjects still qualified, and this number further decreased to 17% when a functional impairment criterion was applied (GAF of at least 45). The pool of eligible subjects shrank to 0.6% (n=2) when the rest of the inclusion criteria were applied

including failure of both pharmacotherapy and CBT. Once exclusion criteria were applied, none of the subjects qualified for DBS.

Across all the above cited studies, severity of OCD symptoms was measured with the Y-BOCS tool. The threshold for study inclusion ranged from a lower limit of 24 (Abelson, 2002) to a high of 31 (Tyagi, 2019). A study published by Mancebo (2008) investigating the correlates of OCD with occupational disability concluded that the most powerful predictor of occupational disability was the severity of OCD. Specifically, their results "indicated that with each standard deviation increase on the Y-BOCS (5.83 points), the odds of occupational disability increased by a factor of 2.26." They reported that the average Y-BOCS score for occupationally disabled individuals was 26.53.

In 2021, the Congress of Neurological Surgeons (Staudt, 2021) published an update to the 2014 systematic review and evidence-based guidelines for deep brain stimulations for obsessive-compulsive disorder (Hamani, 2014). Their analysis indicated that there was Level I evidence, based on Mallet and colleagues (2008) discussed above, supporting the use of bilateral subthalamic nucleus DBS for the treatment of medically refractory OCD. These are their recommendations:

- It is recommended that clinicians utilize bilateral subthalamic nucleus DBS over best medical management for the treatment of patients with medically refractory OCD (Level I).
- Clinicians may use bilateral nucleus accumbens or bed nucleus of stria terminalis DBS for the treatment of patients with medically refractory OCD (Level II).

There is insufficient evidence to make a recommendation for the identification of the most effective target.

The available evidence addressing DBS for OCD, while limited to trials with modest populations and methods, shows that this treatment can provide significant benefits for a prudently selected population of severely-affected individuals with refractory OCD. The available studies have included extensive inclusion and exclusion criteria to assure that this treatment has been used only for individuals most likely to benefit, least likely to suffer from adverse events, and for whom all other less invasive options have been attempted and failed. While there remains substantial risk of adverse events, the demonstrated improvements in the severity of OCD symptoms may warrant selection of this treatment option for individuals with severe functional impairment and the absence of contraindications.

Deep Brain Stimulation for Epilepsy

DBS has been proposed as a treatment for medically refractory epilepsy that persists in severity and/or frequency despite a reasonable trial of two or more antiepileptic medications, as an alternative to resective surgery and when cortical stimulation is not appropriate.

Results from the large-scale Stimulation of the Anterior Nuclei of Thalamus for Epilepsy (SANTE) trial, a double-blind RCT of DBS for epilepsy, were reported by Fisher (2010). This study used a standard DBS device (Medtronic Mode 3387) stimulating the anterior nuclei. All subjects underwent DBS implantation followed by 3 months of randomized and blinded active stimulation (n=54) or no stimulation (n=55), then followed by 9 months of active stimulation for all subjects. A total of 110 subjects had DBS electrode implantation. One subject in the active group was not included in the data analysis and no explanation for this was provided in the article. Both the active and

control groups demonstrated significant decreases in seizure activity through the blinded period. However, the control group trended towards baseline levels at the end of the third month. The active group had a sustained and significant decrease in seizure activity (p=0.0017). A statistically significant difference between groups was only seen in the third month, in favor of the stimulation group (p=0.0023). Changes in additional outcome measures did not show significant differences between groups. During the blinded phase, the frequency of complex partial seizures improved more in the stimulation group vs. controls (p=0.041). Additionally, seizure-related injuries occurred more in controls vs. stimulated subjects (26% vs. 7%; p=0.01). No differences were noted in subjects with prior treatment of vagus nerve stimulation. At completion of the blinded phase, 108 (98.1%) subjects entered the open-label phase. The median seizure frequency percent change from baseline for subjects with at least 70 diary days prior to the visit was -41% (n=99) at 13 months and -56% (n=81) at 25 months. The 50% responder rate at 13, 25, and 37 months was 43%, 54% and 67%. Through 13 months, 808 adverse events were reported in 109 participants; 55 events were categorized as serious and 238 were considered device-related. The most common device-related events were paresthesias (18.2%), implant site pain (10.9%), and implant site infection (9.1%). Five deaths were reported in the follow-up period, including 3 from sudden unexplained death in epilepsy (SUDEP), 1 subject from unobserved drowning in a bathtub, and 1 suicide. None of the deaths were judged device-related by center investigators. During the blinded phase, the stimulation group reported more adverse events relating to depression (8 vs. 1) and memory impairment (7 vs. 1). Subjects in the stimulation group experienced fewer seizure-related injuries (7.4%) vs. the control group (25.5%, p=0.01). The authors state that DBS of the anterior nuclei in this population was mostly palliative in nature, but 14 participants (12.7%) became seizure-free for at least 6 months. Additionally, significant benefits were seen in some subjects who were not previously helped by multiple drugs, vagus nerve stimulation (VNS), or epilepsy surgery. Finally, they conclude by stating, "Additional clinical experience may help to establish the best candidates and stimulation parameters, and to further refine the risk–benefit ratio of this treatment." This is especially true considering the significantly increased rate of depression-related adverse events reported in the experimental group. It must be noted that this study only followed 13 subjects past 13 months, mitigating the utility as well as impact of the longer-term data presented.

Salanova and others published a long-term follow-up study of the SANTE trial in 2015. Beginning 13 months following device implantation, 105 subjects receiving active stimulation were followed for an additional 4 years. The authors reported that for subjects with at least 70 diary entries recorded at 1 year (n=99), median change for seizure frequency from baseline decreased by 41% (p<0.001), and by 69% at 5 years (n=59; p<0.001). For the same population, reduction in the most severe type of seizure was 39% at 1 year (p<0.001) and 75% at 5 years (p<0.001). During the 5-year study, 17 of 109 subjects (16%) reported a 6-month seizure-free interval. A 2-year seizure-free interval was reported for 6 of 109 subjects (5.5%). Mean improvement in the Liverpool Seizure Severity Score (LSSS) was 13.4 at 1 year and 18.3 at 5 years (p<0.001 for both). Similarly, results from the Quality of Life in Epilepsy-31 (QOLIE-31) tool improved from baseline by 5.0 points at 1 year and 6.1 points at 5 years (p<0.001 for both). A change of 5 points on this measure is considered clinically significant, and was experienced by 46% and 48% of subjects at 1 and 5 years. Overall, 39 of the 110 subjects (35.5%) experienced some device-related serious adverse events, which predominantly occurred within the first months of implantation. The most common were impact site infection in 10% of subjects and leads not within target area (8.2%). Depression was reported in 32.7% of subjects over 5 years, but only 3 were considered device-related. Memory impairment was reported in 25.5% of subjects. SUDEP was reported in 7 subjects over the 5-year study period, but none were considered device-related by the data monitoring committee. This study demonstrates significant long-term benefit from DBS for individuals with epilepsy, however, this was a relatively small and unblinded study. Further data from larger blinded RCTs are warranted.

Another study using data from the SANTE trial reported on memory and mood outcomes (Tröster, 2017). Neuropsychological assessments were taken at multiple time points throughout the trial, including baseline, 4 weeks, 4 months, 7 months, 13 months, and yearly up to 7 years (n=67, 61% of the original study cohort). During the blinded phase, depression was reported in 14.8% of active group subjects vs. 1.8% of control group subjects ($p<0.016$), and adverse memory events were reported in 13.0% of active group subjects vs. 1.8% of control group subjects ($p=0.032$). For subjects with depression, 72% had reported prior depression, and 23% experienced new depression symptoms. In subjects with adverse memory events in the blinded phase, prior visual memory events were reported in half of subjects who reported having visual memory events and 37.5% of subjects reported experiencing verbal memory events had prior verbal memory events. Interestingly, while 66% of subjects reporting depression in the active group had a prior history of depression diagnoses, none of these subjects complained of depression during the baseline observation period or unblinded phase. Likewise, none of the subjects reporting memory events experienced them outside of the blinded phase. Also, during the blinded phase, presence of a "confusional state" was reported in 7.4% of active group subjects vs. 0% of control group subjects and "anxiety" was reported in 9.3% of active group subjects vs. 1.8% of control group subjects, but none of these comparisons were statistically significant. The authors concluded that prior depression diagnosis might heighten risk of a depression adverse event within 4 months of surgery, but those without presurgical memory impairment may be more at risk for experiencing memory adverse events. Additionally, for the cohort followed for the full 7 years, they report no significant cognitive declines, neurobehavioral problems (for example, apathy, disinhibition), subjective cognitive declines, or affective distress (depressive and anxious symptoms).

Based on the SANTE trial data, the FDA granted pre-market approval on April 27, 2018 to the Medtronic DBS Therapy System for the treatment of epilepsy with bilateral stimulation of the anterior nucleus of the thalamus (ANT) as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications. As noted above, the SANTE trial data has some significant methodological flaws, and the rates of depression and other adverse effects remain a concern.

In a meta-analysis by Meissner (2013) investigating the impact of sham vs. placebo treatments in studies of DBS for epilepsy, the authors reported that both sham surgical and acupuncture procedures provided significantly more placebo effect than oral placebo. They commented that clinicians need to remember that a relevant part of the overall effect they observe in practice might be due to nonspecific effects. This is apparently true for these studies in the short-term. However, in the Fisher study, the placebo/sham effect mostly disappeared by the end of the 3 month blinded phase in the control groups.

In 2018 Järvenpää published a report of psychiatric adverse events in a series of 22 subjects treated with DBS. Of the 22 subjects, 4 were reported to have had significant mood or psychiatric adverse events, 2 with prior history of depression and 2 without. The onset of adverse events varied considerably, occurring at 2 days through 5 years after active stimulation was initiated. The authors reported that in the 3 subjects with no prior history of mood or psychiatric conditions, altering DMS treatment parameters completely alleviated the symptoms. In the fourth subject, who had a prior history of depression and aggression, symptoms were decreased with parameter adjustments and medical management, but were not completely resolved. All 4 subjects experienced significant decreases in seizure activity throughout their treatment, with sustained benefit following adverse event-related adjustments. This study

indicates that while mood and psychiatric adverse events are a concern with DBS treatment for epilepsy, with proper monitoring and management they can be alleviated or significantly reduced.

Herman and colleagues (2019) reported the results of another small double-blinded RCT investigating the safety and efficacy of DBS in 18 subjects suffering from focal, pharmacoresistant epilepsy. Subjects were assigned to either active or sham treatment. The duration of this trial was 12 months, but subjects were provided their randomized treatment only for the first 6 months. All subjects received active treatment for the second 6-month period. The authors reported no significant differences between groups at the end of the blinded 6 month period. During the open active vs. treatment phase at 6-12 months, there was a significant 22% reduction in the frequency of all seizures vs. baseline (p=0.009). Four subjects had ≥ 50% reduction in total seizure frequency, and 5 subjects had a ≥ 50% reduction in focal seizures at the 12 month time point. No increased effect over time was shown. LSSS at 6 months showed no significant difference between groups, but a small, significant reduction in LSSS was found when all subjects had received stimulation for 6 months.

While the available published peer-reviewed evidence addressing the use of DBS for epilepsy is limited mostly to the SANTE trial results, use of this treatment approach has continued and clinical experience has been gained. As a result, there is a growing body of expert experience and opinion addressing the complications noted above, specifically the concerns regarding the incidence of SUDEP and depression. Expert opinion over the past decade has evolved to see SUDEP risk following DBS initiation as no greater than the SUDEP risk for individuals with medically refractory seizures. Similarly, the concerns regarding depression and mood disorders have been more clearly elucidated with the publication by Tröster and colleagues. With that evidence it has been made clear that specific populations may suffer additional risk of depression or mood disturbances with DBS treatment. However, in the clinical setting there must be an assessment of balancing the risks due to insufficiently treated epilepsy vs. the risks associated with depression and mood disturbances, and the predominant current consensus is that the risks posed by insufficiently treated epilepsy are greater. In summary, the population with medically refractory epilepsy for whom DBS has been proposed suffer from significant morbidity and mortality unrelieved by medical therapy. While some may be candidates for cortical stimulation, many are not. Additionally, resective surgical procedures may be an available option for some, but the use of less invasive and irreversible approaches should be made available.

Deep Brain Stimulation for Other Conditions

Tye and colleagues (2009) investigated the effectiveness of DBS in treatment-resistant depression, OCD, and Tourette syndrome (TS). The authors found that DBS treatment for TS was largely dependent upon electrode placement. One small study (n=5) found that bilateral thalamic electrode placement reduces tic frequency and severity in refractory TS (Maciunas, 2007). Other DBS electrode implantation targets for TS include the centromedian thalamic region (Okun, 2012; Servello, 2008) and the globus pallidus (Diederich, 2005).

In 2009, Porta reported the findings of a case series study involving 18 subjects who underwent bilateral thalamic DBS for TS. At the 24 month follow-up point, there was a marked reduction in tic severity (p=0.001), improvement in obsessive-compulsive symptoms (p=0.009), anxiety symptoms (p=0.001), depressive symptoms (p=0.001), and subjective perception of social functioning/quality of life (p=0.002) in 15 of 18 subjects. There were no substantial differences on measures of cognitive functions before and after DBS. The authors concluded by stating, “Controlled

studies on larger cohorts with blinded protocols are needed to verify that this procedure is effective and safe for selected patients with TS."

Ackermans and colleagues (2011) noted that since 1999, 10 different brain areas have been described as a target for deep brain stimulation in Tourette syndrome. They conducted a study of 8 individuals in a double-blind, randomized cross-over trial using reduction of tic severity as the primary outcome. After surgery, the subjects were randomly assigned to 3 months stimulation followed by 3 months OFF stimulation (Group A) or vice versa (Group B). The cross-over period was followed by 6 months ON stimulation. Tic severity during ON stimulation was significantly lower than during OFF stimulation, with substantial improvement (37%) on the Yale Global Tic Severity Scale (mean 41.1 ± 5.4 versus 25.6 ± 12.8; p=0.046). The authors concluded that these preliminary findings suggest efficacy of DBS for tic symptoms in TS; however, further RCTs on other targets are urgently needed since the optimal DBS target for TS is still unknown.

Welter (2017) published the results of a double-blind RCT involving 17 subjects with severe medically refractory Tourette syndrome who were treated with bilateral implantation of a deep brain stimulator with electrodes to the anterior globus pallidus. Subjects were randomly assigned in a 1:1 fashion to either active (n=8) or sham stimulation (n=9). At 2 months following implantation, all subjects had their stimulators activated to determine the study settings. One month later subjects were randomized to their treatment group and followed in a blinded fashion for an additional 3 months. After that period, all subjects had their devices activated in an open-label fashion for an additional 6 months. Medication regimens were continued during the study. A total of 16 subjects completed the double-blind study period. The authors reported no significant differences between groups at 3 months regarding Yale Global Tic Severity Scale (YGTSS) scores (p=1.0). During the open-label phase, YGTSS scores improved significantly in all subjects (p=0.23). Improvement of 25% or more in YGTSS scores from baseline to the end of the open-label phase was noted in 12 of the 16 completing subjects (p=0.0017). At the end of the open-label phase the stimulators were turned off for 72 hours, at which time mean YGTSS scores decreased 75.7% (p=0.02). During the blinded phase, no significant differences were noted between groups regarding motor or vocal tic YGTSS subscales or any other measures. Between baseline and the end of the open-label phase, significant differences in the motor and vocal tic YGTSS subscales, the Rush Video Rating Scale (RVRS), GAF, the MADRS, and Hospital Anxiety and Depression Scale (HADS) (anxiety), but not in CGI, the Brief Anxiety Scale (BAS), the HADS (depression), the Y-BOCS, the Stroop interference index, Social Adjustment Scale Self- Reported (SAS-SR), or SF-36 scores. A total of 15 serious adverse events were reported in 13 (68%) subjects, including infections leading to removal of the stimulator and electrodes in 4 (21%) subjects. Transient headaches (n=5) and pain along the scars (n=2) were also reported. Adverse events related to stimulation across both groups were reported in 17 subjects, including increased tic severity and anxiety, depressive symptoms, dysarthria, sleep disorder, and imbalance or abnormal movements resembling dyskinesia that resolved rapidly after stimulator adjustments. The authors concluded that 3 months of DBS is insufficient to decrease tic severity for individuals with Tourette's syndrome and further study was needed. Also in 2017, Martinez-Ramirez and colleagues reported an analysis of data from 185 subjects with Tourette syndrome included in the prospectively collected International Deep Brain Stimulation Database and Registry who were treated with bilateral DBS. Surgical selection was made using local evaluations and recommendations, with no standardized inclusion or exclusion criteria. Location of electrodes was likewise not standardized, with stimulation occurring at the centromedian thalamic region (n=93), anterior globus pallidus internus (n=41), posterior globus pallidus internus (n=25), and anterior limb of internal capsule (n=4). The authors reported that the mean total YGTSS score improved from 75.01 at baseline to 41.19 at 1 year (p<0.001). The mean motor tic subscore improved from 21.00 at baseline to 12.91 after 1 year (p<0.001), and the mean phonic tic subscore improved from 16.82 at

baseline to 9.63 at 1 year (p<0.001). The adverse event rate was 35.4% (56 of 158 subjects), with reports of intracranial hemorrhage (n=2), infection (n=5), and lead explantation (n=1). The most common stimulation-induced adverse effects were dysarthria (n=10) and paresthesia (n=13). The authors concluded that DBS was associated with symptomatic improvement in individuals with Tourette syndrome, but also with important adverse events.

The European Clinical Guidelines for Tourette Syndrome and Other Tic Disorders. Part IV: Deep Brain Stimulation (2011) stated that:

> …Of the 63 patients reported so far in the literature 59 had a beneficial outcome following DBS with moderate to marked tic improvement. However, randomized controlled studies including a larger number of patients are still lacking. At present time, DBS in TS is still in its infancy.
> …However, among the European Society for the Study of Tourette Syndrome (ESSTS) working group on DBS in TS, there is general agreement that, at present time, DBS should only be used in adult, treatment resistant, and severely affected patients. It is highly recommended to perform DBS in the context of controlled trials.

Additional uses for DBS are being investigated. For example, in psychosurgery there has been a shift of interest away from ablative techniques and toward deep brain stimulation. However, most studies of DBS for depression and anorexia are few and involve small numbers of subjects (Bergfeld, 2016; Lipsman, 2013, Sachdev, 2009; Schlaepfer, 2013; Wu, 2013). Patel and colleagues (2011) reported a case study using DBS for treatment of severe, refractory hypertension. In 2011, the National Institute for Health and Clinical Excellence (NICE) published DBS assessments in the treatment of trigeminal neuralgia and chronic pain syndromes. They found that the available evidence does not support this use.

In 2015 Dougherty and colleagues published the results of a 24-month sham-controlled RCT involving 30 subjects with treatment resistant depression treated with DBS or sham DBS (n=15 per group). The authors reported no significant differences in response rate between groups (20% vs. 14.3%, respectively). Results from the MADRS demonstrated no significant differences throughout the 16-week controlled phase of the trial. In 2017 a larger 6-month sham-controlled RCT involving 90 subjects was published by Holtzheimer and others. As with the prior study, no statistically significant difference in response was reported (20% in the active group vs. 17% in the sham group). Serious adverse events were experienced by 28 subjects (40 events total), with 8 deemed to be related to the study device or surgery. The findings of these studies demonstrated no benefit to DBS for treatment resistant depression.

Deep brain stimulation is also being studied as a treatment for tremors from other causes including, but not limited to, multiple sclerosis (MS), trauma, and degenerative disorders. In addition, DBS is being investigated to determine if functional improvement is achieved and maintained for other conditions such as chronic cluster headache, cerebral palsy and Tourette syndrome (TS).

Cortical Stimulation

The RNS® System (NeuroPace, Mountain View, CA) consists of a cranially implanted, programmable cortical neurostimulator that senses and records brain activity through electrode-containing leads that are placed at the seizure focus. The device provides what the manufacturer refers to as “responsive cortical stimulation,” which senses

and records seizure activity and responds according to a pre-set program. The system is intended to reduce the frequency of seizures in individuals with medically refractory epilepsy that persists in severity and/or frequency despite a reasonable trial of two or more antiepileptic medications. On November 14, 2013, the RNS System was approved through the PMA (pre-market approval) process by the FDA with the following indication:

> …as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.

The RNS system was approved on the basis of data from three trials; an initial Feasibility study, the Pivotal Trial, and a Long Term Treatment Investigation trial (LTT). In the Feasibility study, the initial 4 subjects were involved in an open-label protocol. The subsequent 61 subjects were enrolled in a double-blind RCT in which subjects received active or sham treatments. The results of this study have been presented in conjunction with the results of the other two studies in the Summary of Safety and Effectiveness data presented to the FDA, but have not been reported separately in a peer-reviewed published paper. As a result, no conclusions can be drawn based on the results of this study alone.

The Pivotal Trial results were reported by Morrell (2011). This study involved the use of the RNS system in a double-blind RCT that initially enrolled 240 subjects. A total of 49 subjects were excluded prior to implantation, leaving 191 subjects for analysis. Inclusion criteria were 18-70 years of age, partial onset seizures refractory to at least two trials of anti-epileptic drugs, had experienced at least three disabling seizures per month and had either one or two epileptogentic regions localized. All subjects underwent implantation of the RNS system followed by a 1-month break-in period followed by randomization. Subjects were assigned to either active or sham therapy, and followed for the 12-week blinded treatment phase, then an 84-week open-label period where all subjects received active therapy. The authors reported that the blind was successfully maintained (blinding index 0.5727). Both groups experienced a reduction in mean seizure frequency during the first post-implant month prior to randomization. However, this reduction abated during the blinded period in the sham group until, in the final month of the blinded period, seizure frequency approached pre-implant levels. Mean seizure frequency was significantly reduced in the treatment group vs. the sham group ($p=0.012$) during the blinded period. The responder rate (percentage of subjects with a $\geq$ 50% reduction in seizures) over the blinded period was not significant overall, with 29% in the treatment group responding vs. 27% in the sham group. However, seizure-free days over the first month continued to increase in the treatment group but declined for the sham group. By the third month, the treatment group had 27% fewer days with seizures vs. 16% fewer days in the sham group ($p=0.048$). During the open-label period, the sham group demonstrated a statistically significant reduction in mean seizure frequency compared to the pre-implant period ($p=0.04$). Across all subjects, the seizure reduction was sustained, and even improved, over time. The responder rate at 1 year post-implant was 43% (n=177) and 46% (n=102) at 2 years. As of the data cutoff date, 13 subjects (7.1%) were seizure-free over the most recent 3-month period. The Quality of Life in Epilepsy-89 (QOLIE-89) assessment tool overall t scores were significantly improved in both groups at the end of the blinded period ($p=0.040$), 1 year ($p<0.001$) and 2 years ($p=0.016$). During the blinded period, there was no difference between the treatment and sham groups in the frequency of cognitive adverse events, or any neuropsychological measure through 2 years. No adverse

changes in mood inventories were reported at any time point in the study. The serious adverse event rate for medical and surgical events for the first 84 weeks was 18.3%. This compares favorably to comparator rates for DBS. There was no difference between the treatment and sham groups in the percentage of subjects with mild or serious adverse events over the blinded period, and included intracranial hemorrhage due to surgical complications and subdural hematomas attributed to seizure-related head trauma. Six subjects died, but none were attributed to responsive cortical stimulation treatment. The authors conclude with:

> Improvements in QOL overall and in domains related to health concerns, social functioning, and cognition support the clinical meaningfulness of the treatment response. Safety was acceptable compared to alternative and comparable procedures and to the risks of frequent seizures. Stimulation was well-tolerated and there were no adverse effects on cognition or mood. Given these findings, responsive cortical stimulation may provide another much-needed treatment option for persons with medically intractable partial seizures.

The final part of the FDA submission data came from the LTT, which was composed of 57 subjects who completed the Feasibility trial and another 173 subjects who completed the Pivotal Trial. These subjects are being followed for a maximum of 7 years, and the study is ongoing.

The first published report of data from the LTT was made available in 2015 (Bergey, 2015). This report included data from 191 subjects who have completed data at the 6-year cutoff point, but data are presented based on the entire subject pool of 256. The median reduction in seizures was 60% at 3 years and 66% at 6 years. The responder rates at the same time points were 58% and 59%. Adjusted response rates taking into account withdrawals at the same time points were 58% and 56%. Based on data from the last 3 months of the collection period, 84% of subjects had some improvement, 60% had 50% or greater reduction in seizure frequency, and 16% were seizure free. Only 8% had a 50% or greater increase in seizure activity. Over one-third of subjects experienced a 3-month seizure-free interval, and 23% experienced one of 6 months or longer. QOLIE-89 measures through year 5 continued to improve significantly ($p<0.001$). Serious events were reported in 2.5% or more of the subjects at any time during the study period. Three intracranial hemorrhages were reported at 18 months, 2.5 years, and 2.8 years following device implantation. Death was reported for 11 subjects, including 2 suicides, 1 status epilepticus, 1 lymphoma, and 7 possible SUDEP. The device was off at the time of 2 SUDEP deaths. These results are promising and demonstrate continued significant benefit to the use of the RNS system in subjects with epilepsy.

In 2014, Heck and colleagues published the final 2-year results of the Pivotal trial. The percent change in seizures at the end of the blinded period was -37.9% in the active and -17.3% in the sham group ($p=0.012$). The median percent reduction in seizures in the open-label period was 44% at 1 year and 53% at 2 years, which represents a progressive and significant improvement with time ($p<0.0001$). The authors reported no differences between groups regarding the rate of serious adverse events, which were consistent with the known risks of an implanted medical device, seizures, and of other epilepsy treatments. There were no adverse effects on neuropsychological function or mood.

Use of the RNS system for the treatment of mesial temporal lobe (MTL) epilepsy was evaluated in a retrospective study involving data from 111 subjects who were involved in the Feasibility (n=16), Pivotal (n=95) studies, and LTT studies (92 Pivotal subjects continued into the LTT) (Geller, 2017). The mean follow-up at the time of data cutoff was 6.1 ± 2.2 years. Subjects had one to four leads placed during the initial procedure, with one lead (n=1), two leads (n=92), three leads (n=4) or four leads placed (n=14). Only depth leads were placed in 76 subjects, 29 had both depth

and strip leads, and 6 had only strip leads. The authors reported that disabling seizures were reduced by a median 66.5% at 6 years, and the 50% responder rate reached 64.6%. No seizures were reported by 20.8% of subjects in the last 3 months. Over the entire open-label period, 45% of subjects reported seizure-free intervals lasting ≥ 3 months, 29% lasting ≥ 6 months, and 15% lasting ≥ 1 year. There was no difference in seizure reduction in subjects with and without mesial temporal sclerosis (MTS, p=0.42), bilateral MTL onsets (p=0.97), prior resection (p=0.54), prior intracranial monitoring, and prior VNS (p=0.78). There were only two device-related (related or uncertain as categorized by the investigator) serious adverse events reported in 13 of subjects, including superficial soft tissue implant-site infection and device lead damage. Implant-site skin erosion was reported in 2 subjects. Lead replacement due to lead damage occurred in 7 subjects. Three subjects had a serious AE related to intracranial hemorrhage, and two were categorized as device related. A total of 6 deaths were reported, 1 suicide and 5 attributed to possible (n=2), probable (n=1), or definite (n=2) SUDEP. Other adverse events reported include photopsia (n=16), memory impairment (n=7), and depression (n=2).

A similar study was described by Jobst in 2017 involving 126 subjects from the Pivotal (n=45) and LTT studies (n=81) with frontal-onset seizures and leads in either Broca's or Wernicke's areas were included. The mean follow-up at the time of data cutoff was 6.1 ± 2.6 years. Seizure data were available for 120 subjects with > 1 year of follow-up, 87 had at least 6 years of follow-up. The reported median percent reduction in seizures was 44% after 2 years, 61% after 5 years, and 76% after 6 years. During the open-label period, 37% of subjects had at least one seizure-free interval lasting ≥ 3 months, 26% had at least one lasting ≥ 6 months, and 14% had at least one lasting ≥ 1 year. Previous surgery or prior VNS had no impact on seizure reduction results (p=0.12 and p=0.20, respectively). Both subjects with and without structural lesions experienced a reduction in seizure frequency, and the reduction was greater in subjects with a structural lesion than in those without, and the difference between these groups was significant over the entire follow-up (p=0.02). Serious adverse events related to intracranial hemorrhage were reported in 9 subjects, with 6 attributed to seizure-related head trauma. Two subjects had cerebral hemorrhages several years after implantation, with one considered device related. Serious infection-related adverse events were reported in 13 subjects, with 9 resulting in explantation of the stimulator and 6 in explantation of the leads as well. Two subjects developed scalp erosions over the neurostimulator. Death was reported for 5 subjects with 1 suicide, 1 due to status epilepticus, 1 due to lymphoma, and 2 attributed to definite SUDEP.

Devinsky (2018) reported the results of a retrospective study investigating the incidence of SUDEP in 707 subjects implanted with the RNS system. The authors reported that there were 14 all-cause total deaths in the study cohort with 2208 years of post-implantation follow-up data. There were two possible, one probable and four definite SUDEP events, resulting in an overall, standardized mortality ratio (SMR) for probable and definite SUDEP of 0.75 (95%, confidence interval [CI], 0.27-1.65). Two subjects who suffered SUDEP did not have their stimulator devices activated at the time of death. The authors reported a SUDEP rate of 2.0/1000 patient stimulation years, and state that this is, "is favorable relative to treatment-resistant epilepsy patients randomized to the placebo arm of add-on drug studies or with seizures after resective surgery."

In 2020, Ma and colleagues reported the results of a multicenter retrospective cohort study of participants (n=30) with drug-resistant focal epilepsy and a regional neocortical seizure-onset zone (SOZ) delineated by intracranial monitoring who were treated with the RNS system for at least 6 months. The changes in seizure frequency were assessed relative to the preimplant baseline, and correlation between clinical outcome and stimulation parameters were evaluated. Participants were age 9 to 42 years, with mean duration of epilepsy of 14.2 ± 10.3 years, and a varied epilepsy etiology. There were 5 participants that underwent a partial resection of the SOZ concurrent with

RNS system implantation. Median follow-up was 21.5 months. Median reduction in clinical seizure frequency was 75.5% (interquartile range 40% to 93.9%). There was no significant difference in outcome between participants treated with and without concurrent partial resection. Most participants were treated with low charge densities (1-2.5 $\mu C/cm^2$). Seizure reduction was not correlated with interlead distance, maximum charge density, treatment duration, or concurrent partial resection. The study's limitations include a modest sample size, retrospective design, heterogeneity of lead locations, and antiepileptic drug adjustments during the study period.

Responsive cortical stimulation with the RNS system has been demonstrated to be safe and effective in select individuals with partial onset seizures who have undergone diagnostic testing that localized no more than two epileptogenic foci, are refractory to two or more antiepileptic medications, and are currently having an average of three or more disabling seizures per month. Studies have shown significant improvements in seizure frequency.

The use of cortical stimulation has been investigated in a small number of studies for a variety of indications including chronic pain syndromes. All of these studies were case series with low statistical power. Data from well-designed and conducted trials is needed to understand the clinical utility of cortical stimulation for conditions other than those discussed above.

Cerebellar Stimulation/Pacing

Cerebellar stimulation/pacing is electrical stimulation using surgically implanted electrodes on the surface of the cerebellum and has been proposed as one way to treat some neurological disorders.

In 2019 Koch reported the results of a small double-blind RCT involving the use of cerebellar pacing in 34 subjects with post-stroke hemiparesis. Subjects were assigned to treatment with either cerebellar intermittent θ-burst stimulation (CRB-iTBS) applied over the cerebellar hemisphere ipsilateral to the affected body side immediately before physiotherapy daily during 3 weeks, or sham treatment. Improvement of gait and balance functions was reported in the treatment group, demonstrated by improvement in Berg Balance Scale score ($p<0.001$), but no overall treatment-associated differences were noted in the Fugl-Meyer Assessment ($p>0.05$) or Barthel Index scores ($p>0.05$). Subjects in the treatment group were also reported to have demonstrated a reduction of step width vs. control subjects ($p<0.05$), as well as an increase of neural activity over the posterior parietal cortex. These results are promising, but data from larger trials are needed to provide generalizable results.

There is inadequate information available to make an assessment of the clinical usefulness of this treatment method.

Background/Overview

Various forms of electrical stimulation have been investigated as an alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy for neuroelectrical conditions. The technique using deep brain stimulation (DBS) has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of essential tremor, and tremor associated with Parkinson's disease (PD). DBS has also been investigated in individuals with primary dystonia, defined as a neurological movement disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, contorted and painful movements or postures and which is unrelated to any other neurological condition. Treatment options for dystonia include oral or injectable

medications (i.e., botulinum toxin) and destructive surgical or neurosurgical interventions (i.e., thalamotomies or pallidotomies) when conservative therapies fail.

Deep brain stimulation involves the stereotactic placement of an electrode into the brain (i.e., thalamus, globus pallidus, or subthalamic nucleus). The electrode is initially attached to a temporary transcutaneous cable for short-term stimulation to validate treatment effectiveness. Several days later, the individual returns to surgery for permanent subcutaneous implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. The electrode is typically implanted unilaterally on the side corresponding to the most severe symptoms. However, the use of bilateral stimulation using two electrode arrays has also been investigated in individuals with bilateral, severe symptoms.

After implantation, noninvasive programming of the neurostimulator can be adjusted to the individual's symptoms. This feature may be important for individuals with PD, whose disease may progress over time, requiring different neurostimulation parameters. Setting the optimal neurostimulation parameters may involve the balance between optimal symptom control and appearance of side effects of neurostimulation, such as dysarthria, disequilibrium, or involuntary movements.

Cortical stimulation is a newer technology proposed for the treatment of epilepsy. The RNS System (NeuroPace, Inc., Mountain View, CA) is a device used for this type of treatment. The RNS System involves implantation of electrodes onto the surface the brain near areas associated with seizure activity. Those electrodes are then attached to a control/generator unit which is also implanted in the head. The control unit monitors and records electrical activity of the brain and provides electrical stimulation when needed. Following a trial period, the initial brain activity record is evaluated by a doctor. The record is used to identify the individual's unique pre-seizure electrical brain activity patterns and to set the RNS device to recognize and react to those patterns. Once the recognition parameters are set, the device monitors brain activity for the pre-set patterns of electrical activity. If those patterns are detected the device activates to provide stimulation through the electrodes with the goal of preventing a seizure.

Cerebellar stimulation or pacing is a similar technique to DBS but works in the cerebellar portion of the brain. There is little information about the use of this technology in humans.

Definitions

Cerebellar stimulation/pacing: A proposed treatment of neurological disorders that involves electrical stimulation of the cerebellum part of the brain.

Dystonia: Covers a diverse group of movement disorders, all of which are characterized by involuntary muscle contractions that may cause twisting and repetitive movements or abnormal postures; dystonia is the most severe form of a group of movement disorders called dyskinesias.

Essential tremor (ET): A chronic, incurable condition with unknown cause characterized by involuntary, rhythmic tremor of a body part, most typically the hands and arms.

Globus pallidus interna (Gpi): A part of the brain involved with movement.

Humanitarian Device Exemption (HDE): Similar to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose and does not pose an unreasonable or significant risk of illness or injury. The use of the device is limited to 4000 or less individuals per year.

Medically refractory epilepsy: When an individual has epilepsy that persists in severity and/or frequency despite a reasonable trial of two or more antiepileptic medications.

Multiple sclerosis: A condition of the nervous system that results in a wide variety of symptoms.

Non-epileptic seizures: A condition where a person experiences symptoms similar to an epileptic seizure, but no unusual electrical activity in the brain is present. Such non-epileptic seizures may be caused by mental stress or a physical condition.

Parkinson's disease: A progressive, incurable disease caused by the slow continuous loss of nerve cells in the part of the brain that controls muscle movement.

Post-traumatic dyskinesia: A condition where movement is altered or absent due to a traumatic injury.

Primary dystonia: A type of dystonia which is not due to a secondary cause such as stroke, cerebral palsy, tumor, trauma, infection, multiple sclerosis, medications, or a neurodegenerative disease.

Secondary dystonia: A type of dystonia which is associated with a known, acquired cause or additional neurologic abnormality where symptoms of involuntary muscle contractions are related to other conditions such as stroke, trauma, toxic substance exposure or asphyxia.

Subthalamic nucleus (STN): A part of the brain involved with movement.

Tourette's syndrome or Tourette syndrome (TS): A neurological disorder characterized by multiple facial and other body tics, usually beginning in childhood or adolescence and often accompanied by grunts and compulsive utterances, such as interjections and obscenities: TS is also called Gilles de la Tourette syndrome.

Unified Parkinson's Disease Rating Scale (UPDRS): UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease and is made up of three sections: 1) mentation, behavior and mood, 2) activities of daily living and 3) motor sections evaluated by interview.

Ventralis intermediate nucleus of the thalamus (Vim): A part of the brain involved with movement.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider

reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Deep Brain Stimulation
When services may be Medically Necessary when criteria are met:

CPT	
61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
61864	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array
61867	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
61868	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Incision and subcutaneous placement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
HCPCS	
C1767	Generator; neurostimulator (implantable), nonrechargeable
C1820	Generator; neurostimulator (implantable), non high-frequency with rechargeable battery and charging system
C1787	Patient programmer, neurostimulator
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension

L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

ICD-10 Procedure

	For the following codes when specified as deep brain stimulator leads:
00H00MZ-00H04MZ	Insertion of neurostimulator lead into brain [by approach; includes codes 00H00MZ, 00H03MZ, 00H04MZ]
00H60MZ-00H64MZ	Insertion of neurostimulator lead into cerebral ventricle [by approach; includes codes 00H60MZ, 00H63MZ, 00H64MZ]

ICD-10 Diagnosis

F42.2-F42.9	Obsessive-compulsive disorder
F60.5	Obsessive-compulsive personality disorder
G20.A1-G20.C	Parkinson's disease
G21.0-G21.9	Secondary parkinsonism
G24.1	Genetic torsion dystonia
G24.2	Idiopathic nonfamilial dystonia
G24.3	Spasmodic torticollis
G24.8	Other dystonia
G24.9	Dystonia, unspecified
G25.0	Essential tremor
G40.001-G40.919	Epilepsy and recurrent seizures

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, for deep brain stimulation for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

Cortical Stimulation
When services may be Medically Necessary when criteria are met:

CPT

61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
64999	Unlisted procedure, nervous system [when specified as implantation of cortical neurostimulator]

HCPCS

C1767	Generator; neurostimulator (implantable), nonrechargeable
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each

ICD-10 Procedure

	For the following codes when specified as cortical stimulator leads:
00H00MZ-00H04MZ	Insertion of neurostimulator lead into brain [by approach; includes codes 00H00MZ, 00H03MZ, 00H04MZ]
00H60MZ-00H64MZ	Insertion of neurostimulator lead into cerebral ventricle [by approach; includes codes 00H60MZ, 00H63MZ, 00H64MZ]

ICD-10 Diagnosis

G40.001-G40.919	Epilepsy and recurrent seizures

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, for cortical stimulation for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

Cerebellar Stimulation
When Services are also Investigational and Not Medically Necessary:

CPT

64999	Unlisted procedure, nervous system [when specified as craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebellar]

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. Abelson JL, Curtis GC, Sagher O, et al. Deep brain stimulation for refractory obsessive-compulsive disorder. Biol Psychiatry. 2005; 57(5):510-516.
2. Ackermans L, Duits A, van der Linden C, et al. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. Brain. 2011; 134(Pt 3):832-844.
3. Alonso P, Cuadras D, Gabriëls L, et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. PloS One. 2015; 10(7):e0133591.
4. Anderson WS, Kossoff EH, Bergey GK, Jallo GI. Implantation of a responsive neurostimulator device in patients with refractory epilepsy. Neurosurg Focus. 2008; 25(3):E12.
5. Barcia JA, Avecillas-Chasín JM, Nombela C, et al. Personalized striatal targets for deep brain stimulation in obsessive-compulsive disorder. Brain Stimul. 2019; 12(3):724-734.
6. Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015; 84(8):810-817.
7. Bergfeld IO, Mantione M, Hoogendoorn ML, et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2016; 73(5):456-464.

8. Cif L, El Fertit H, Vayssiere N, et al. Treatment of dystonic syndromes by chronic electrical stimulation of the internal globus pallidus. J Neurosurg Sci. 2003; 47(1):52-55.
9. Denys D, Graat I, Mocking R, et al. Efficacy of deep brain stimulation of the ventral anterior limb of the internal capsule for refractory obsessive-compulsive disorder: a clinical cohort of 70 patients. Am J Psychiatry. 2020; 177(3):265-271.
10. Denys D, Mantione M, Figee M, et al. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. 2010; 67(10):1061-1068.
11. Deuschl, G, Wenzelburger R, Loffler K, et al. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. Brain. 2000; 123(Pt 8):1568-1580.
12. Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. Epilepsia. 2018; 59(3):555-561.
13. Diederich NJ, Kalteis K, Stamenkovic M, et al. Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: a case report. Mov Disord. 2005; 20(11):1496-1499.
14. Dougherty DD, Rezai AR, Carpenter LL, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry. 2015; 78(4):240-248.
15. Fields JA, Troster AI, Woods SP, et al. Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor. J Neurol Neurosurg Psychiatry. 2003; 74(3):305-311.
16. Figuerias-Mendez R, Regidor I, Riva-Meana C, Magarinos-Ascone CM. Further supporting evidence of beneficial subthalamic stimulation in Parkinson's patients. Neurology. 2002; 58(3):469-470.
17. Fisher R, Salanova V, Witt T, et al.; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010; 51(5):899-908.
18. Fraix V, Houeto JL, Lagrange C, et al. Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006; 77(4):443-449.
19. Garnaat SL, Greenberg BD, Sibrava NJ, et al. Who qualifies for deep brain stimulation for OCD? Data from a naturalistic clinical sample. J Neuropsychiatry Clin Neurosci. 2014; 26(1):81-86.
20. Geller EB, Skarpaas TL, Gross RE, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. Epilepsia. 2017; 58(6):994-1004.
21. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord. 2004; 19(9):1020-1028.
22. Goetz CG, Poewe W, Rascol O, Sampaio C. Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. Mov Disord. 2005; 20(5):532-539.
23. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008; 23(15):2129-2170.
24. Goodman WK, Foote KD, Greenberg et al. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. Biol Psychiatry. 2010; 67(6):535-542.
25. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. development, use, and reliability. Arch Gen Psychiatry. 1989a; 46(11):1006-1011.
26. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. II. Validity. Arch Gen Psychiatry. 1989b; 46(11):1012-1016.
27. Greenberg BD, Gabriels LA, Malone D, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry. 2010; 15(1):64-79.

28. Hageman SB, van Rooijen G, Bergfeld IO, et al. Deep brain stimulation versus ablative surgery for treatment-refractory obsessive-compulsive disorder: A meta-analysis. Acta Psychiatr Scand. 2021; 143(4):307-318.
29. Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia. 2014; 55(3):432-441.
30. Herrman H, Egge A, Konglund AE, et al. Anterior thalamic deep brain stimulation in refractory epilepsy: A randomized, double-blinded study. Acta Neurol Scand. 2019; 139(3):294-304.
31. Holland MT, Trapp NT, McCormick LM, et al. Deep brain stimulation for obsessive-compulsive disorder: a long term naturalistic follow up study in a single institution. Front Psychiatry. 2020; 11:55.
32. Holtzheimer PE, Husain MM, Lisanby S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. Lancet Psychiatry. 2017; 4(11):839-849.
33. Huff W, Lenartz D, Schormann M, et al. Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: outcomes after one year. Clin Neurol Neurosurg. 2010; 112(2):137-143.
34. Huys D, Kohl S, Baldermann JC, et al. Open-label trial of anterior limb of internal capsule-nucleus accumbens deep brain stimulation for obsessive-compulsive disorder: insights gained. J Neurol Neurosurg Psychiatry. 2019; 90(7):805-812.
35. Järvenpää S, Peltola J, Rainesalo S, et al. Reversible psychiatric adverse effects related to deep brain stimulation of the anterior thalamus in patients with refractory epilepsy. Epilepsy Behav. 2018; 88:373-379.
36. Jimenez F, Nicolini H, Lozano AM. Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. World Neurosurg. 2013; 80(3-4):S30.e17-e25.
37. Jobst BC, Kapur R, Barkley GL, et al. Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. Epilepsia. 2017; 58(6):1005-1014.
38. Koch G, Bonnì S, Casula EP, et al. Effect of cerebellar stimulation on gait and balance recovery in patients with hemiparetic stroke: a randomized clinical trial. JAMA Neurol. 2019; 76(2):170-178.
39. Kohl S, Schönherr DM, Luigjes J, et al. Deep brain stimulation for treatment-refractory obsessive compulsive disorder: a systematic review. BMC Psychiatry. 2014; 14:214.
40. Levine CB, Fahrbach KR, Siderowf AD, et al. Diagnosis and treatment of Parkinson's disease: a systematic review of the literature. Evid Rep Technol Assess (Summ). 2003; (57):1-4.
41. Lipsman N, Woodside DB, Giacobbe P, et al. Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a phase 1 pilot trial. Lancet. 2013; 381(9875):1361-1370.
42. Luyten L, Hendrickx S, Raymaekers S, et al. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. Mol Psychiatry 2016; 21:1272-1280.
43. Ma BB, Fields MC, Knowlton RC, et al. Responsive neurostimulation for regional neocortical epilepsy. Epilepsia. 2020; 61(1):96-106.
44. Maciunas RJ, Maddux BN, Riley DE, et al. Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. J Neurosurg. 2007; 107(5):1004-1014.
45. Mallet L, Polosan M, Jaafari N, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008; 359(20):2121-2134.
46. Mancebo MC, Greenberg B, Grant JE, et al. Correlates of occupational disability in a clinical sample of obsessive-compulsive disorder. Compr Psychiatry. 2008; 49(1):43-50.
47. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, et al. Efficacy and safety of deep brain stimulation in Tourette syndrome the international Tourette syndrome deep brain stimulation public database and registry. JAMA Neurol. 2018; 75(3):353-359.

48. Meissner K, Fässler M, Rücker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA Intern Med. 2013; 173(21):1941-1951.
49. Menchón JM, Real E, Alonso P, et al. A prospective international multi-center study on safety and efficacy of deep brain stimulation for resistant obsessive-compulsive disorder. Mol Psychiatry. 2021; 26(4):1234-1247.
50. Merello M, Nouzeilles MI, Kuzis G, et al. Unilateral radiofrequency lesion versus electrostimulation of posteroventral pallidum: a prospective randomized comparison. Mov Disord. 1999; 14(1):50-56.
51. Morrell MJ.; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011; 77(13):1295-1304.
52. Mosley PE, Windels F, Morris J, et al. A randomised, double-blind, sham-controlled trial of deep brain stimulation of the bed nucleus of the stria terminalis for treatment-resistant obsessive-compulsive disorder. Transl Psychiatry. 2021; 11(1):190.
53. Naesström M, Blomstedt P, Bodlund O. A systematic review of psychiatric indications for deep brain stimulation, with focus on major depressive and obsessive-compulsive disorder. Nord J Psychiatry. 2016; 70(7):483-491.
54. Nuttin B, Cosyns P, Demeulemeester H, et al. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet.1999; 354:1526.
55. Obeso JA, Guridi J, Rodriguez-Oroz MC, et al.; Deep Brain Stimulation for Parkinson's Disease Study Group. Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's Disease. N Engl J Med. 2001; 345(13):956-963.
56. Okun MS, Foote KD, Wu SS, et al. A trial of scheduled deep brain stimulation for Tourette syndrome: moving away from continuous deep brain stimulation paradigms. JAMA Neurol. 2013; 70(1):85-94.
57. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology. 2001; 56(11 Suppl 5):S1-S88.
58. Ondo W, Almaguer M, Jankovic J, Simpson RK. Thalamic deep brain stimulation: comparison between unilateral and bilateral placement. Arch Neurol. 2001; 58(2):218-222.
59. Pahwa R, Lyons KL, Wilkinson SB, et al. Bilateral thalamic stimulation for the treatment of essential tremor. Neurology. 1999; 53(7):1447-1450.
60. Patel N, Javed S, Khan S, et al. Deep brain stimulation relieves refractory hypertension. Neurology. 2011; 76(4):405-407.
61. Piper M, Abrams GM, Marks WJ Jr. Deep brain stimulation for the treatment of Parkinson's disease: overview and impact on gait and mobility. NeuroRehabilitation. 2005; 20(3):223-232.
62. Polosan M, Droux F, Kibleur A, et al. Affective modulation of the associative-limbic subthalamic nucleus: deep brain stimulation in obsessive-compulsive disorder. Transl Psychiatry. 2019; 9(1):73.
63. Porta M, Brambilla A, Cavanna AE, et al. Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: two-year outcome. Neurology. 2009; 73(17):1375-1380.
64. Portman AT, van Laar T, Staal MJ, et al. Chronic stimulation of the subthalamic nucleus increases daily on-time without dyskinesia in advanced Parkinson's disease. Parkinsonism Relat Disord. 2006; 12(3):143-148.
65. Rauch, SL. A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. J Neurosurg. 2006; 104:558-565.
66. Raviv N, Staudt MD, Rock AK, et al. A systematic review of deep brain stimulation targets for obsessive compulsive disorder [published online ahead of print, 2020 Jul 2]. Neurosurgery. 2020;nyaa249.
67. Rehncrona S, Johnels B, Widner H, et al. Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. Mov Disord. 2003; 18(2):163-170.

68. Roh D, Chang WS, Chang JW, Kim CH. Long-term follow-up of deep brain stimulation for refractory obsessive-compulsive disorder. Psychiatry Res. 2012; 200(2-3):1067-1070.
69. Roper JA, Kang N, Ben J, et al. Deep brain stimulation improves gait velocity in Parkinson's disease: a systematic review and meta-analysis. J Neurol. 2016; 263(6):1195-1203.
70. Sachdev PS, Chen X. Neurosurgical treatment of mood disorders: traditional psychosurgery and the advent of deep brain stimulation. Curr Opin Psychiatry. 2009; 22(1):25-31.
71. Salanova V, Witt T, Worth R, et al.; SANTE Study Group. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015; 84(10):1017-1025.
72. Schlaepfer TE, Bewernick BH, Kayser S, et al. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry. 2013; 73(12):1204-1212.
73. Schuepbach WM, Rau J, Knudsen K, et al.; EARLYSTIM Study Group. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med. 2013; 368(7):610-622.
74. Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med. 2000; 342(7):461-468.
75. Servello D, Porta M, Sassi M, et al. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. J Neurol Neurosurg Psychiatry. 2008; 79(2):136-142.
76. Tan ZG, Zhou Q, Huang T, Jiang Y. Efficacies of globus pallidus stimulation and subthalamic nucleus stimulation for advanced Parkinson's disease: a meta-analysis of randomized controlled trials. Clin Interv Aging. 2016; 11:777-786.
77. Tröster AI, Meador KJ, Irwin CP, Fisher RS.; SANTE Study Group. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure. 2017; 45:133-141.
78. Tyagi H, Apergis-Schoute AM, Akram H, et al. A randomized trial directly comparing ventral capsule and anteromedial subthalamic nucleus stimulation in obsessive-compulsive disorder: clinical and imaging evidence for dissociable effects. Biol Psychiatry. 2019; 85(9):726-734.
79. Tye SJ, Frye MA, Lee KH. Disrupting disordered neurocircuitry: treating refractory psychiatric illness with neuromodulation. Mayo Clin Proc. 2009; 84(6):522-532.
80. Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med. 2005; 352(5):459-467.
81. Vitek JL, Jain R, Chen L, et al. Subthalamic nucleus deep brain stimulation with a multiple independent constant current-controlled device in Parkinson's disease (INTREPID): a multicentre, double-blind, randomised, sham-controlled study. Lancet Neurol. 2020; 19(6):491-501.
82. Volkmann J, Mueller J, Deuschl G, et al.; DBS study group for dystonia. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. Lancet Neurol. 2014; 13(9):875-884.
83. Volkmann J, Wolters A, Kupsch A, et al.; DBS study group for dystonia. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol. 2012; 11(12):1029-1038.
84. Voon V, Droux F, Chabardes S, et al. Dissociable effects of subthalamic stimulation in obsessive compulsive disorder on risky reward and loss prospects. Neuroscience. 2018; 382:105-114.
85. Weaver F, Follett K, Hur K, et al. Deep brain stimulation in Parkinson disease: a metaanalysis of patient outcomes. J Neurosurg. 2005; 103(6):956-967.
86. Welter ML, Houeto JL, Thobois S, et al.; STIC study group. Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. Lancet Neurol. 2017; 16(8):610-619.

87. Welter ML, Mallet L, Houeto JL, et al. Internal pallidal and thalamic stimulation in patients with Tourette syndrome. Arch Neurol. 2008; 65(7):952-957.
88. Winter L, Saryyeva A, Schwabe K, et al. Long-term deep brain stimulation in treatment-resistant obsessive-compulsive disorder: outcome and quality of life at four to eight years follow-up. Neuromodulation. 2021; 24(2):324-330.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Academy of Neurology. Evaluation of surgery for Parkinson's disease: a report of the Therapeutics & Technology Assessment Subcommittee of the Task Force on Surgery for Parkinson's Disease. Neurology. 1999; 53(9):1910-1921.
2. Centers for Medicare and Medicaid Services. National Coverage Determination for Deep Brain Stimulation for Essential Tremor and Parkinson's Disease. NCD #160.24. Effective April 1, 2003. Available at: http://www.cms.gov/medicare-coverage-database/indexes/ncd-by-chapter-and-section-index.aspx?bc=BAAAAAAAAAAA&. Accessed on November 7, 2022.
3. ClinicalTrials.gov. Effectiveness of deep brain stimulation for treating people with treatment resistant obsessive-compulsive disorder. Identifier: NCT00640133. Available at: https://clinicaltrials.gov/ct2/show/NCT00640133. Accessed on November 7, 2022.
4. Hamani C, Pilitsis J, Rughani AI, et al. Deep brain stimulation for obsessive-compulsive disorder: systematic review and evidence-based guideline sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and endorsed by the CNS and American Association of Neurological Surgeons. Neurosurgery. 2014; 75(4):327-333.
5. Müller-Vahl KR, Cath DC, Cavanna AE, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part IV: deep brain stimulation. Eur Child Adolesc Psychiatry. 2011; 20(4):209-217.
6. Pahwa R, Factor AS, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesias (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006; 66(7):983-995.
7. Rodrigues FB, Duarte GS, Prescott D, et al. Deep brain stimulation for dystonia. Cochrane Database Syst Rev. 2019(1):CD012405.
8. Rughani A, Schwalb JM, Sidiropoulos C, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation for the Treatment of Patients with Parkinson's Disease: Executive Summary. Neurosurgery. 2018; 82(6):753-756.
9. Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev. 2017;(7):CD008497.
10. Staudt MD, Pouratian N, Miller JP, Hamani C, Raviv N, McKhann GM, Gonzalez-Martinez JA, Pilitsis JG. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines for Deep Brain Stimulations for Obsessive-Compulsive Disorder: Update of the 2014 Guidelines. Neurosurgery. 2021; 88(4):710-712.
11. U.S. Food and Drug Administration Center for Devices and Radiological Health. Medtronic Activa® Parkinson's Control Therapy. Premarket Approval. 960009. Rockville, MD: FDA. January 14, 2002. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P960009. Accessed on November 7, 2022.
12. U.S. Food and Drug Administration Center for Devices and Radiological Health. Humanitarian Device Approval. Medtronic Activa® Dystonia Therapy. H020007. Rockville, MD: FDA. April 15, 2003. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf2/H020007A.pdf. Accessed on November 7, 2022.

13. U.S. Food and Drug Administration Center for Devices and Radiological Health. Medtronic DBS System for Epilepsy – P960009/S219. Rockville, MD: FDA. April 27, 2018. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P960009S219. Accessed on November 7, 2022.
14. U.S. Food and Drug Administration Center for Devices and Radiological Health. Humanitarian Device Approval. Medtronic Reclaim™ Deep Brain Stimulation for Obsessive Compulsive Disorder (OCD) Therapy H050003. Rockville, MD: FDA. February 4, 2009. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf5/H050003a.pdf. Accessed on November 7, 2022.
15. U.S. Food and Drug Administration. NeuroPace® RNS® System. P100026- Summary of Safety and Effectiveness Data. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100026B.pdf. Accessed on November 7, 2022.
16. U.S. Food and Drug Administration. RNS® System – P100026. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100026A.pdf. Accessed on November 7, 2022.
17. U.S. Food and Drug Administration. Vercise Deep Brain Stimulation (DBS) System- P150031. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150031A.pdf. Accessed on November 7, 2022.
18. U.S. Food and Drug Administration. Vercise Genus DBS System – P150031/S034. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150031S034. Accessed on November 7, 2022.
19. Wu H, Van Dyck-Lippens PJ, Santegoeds R, et al. Deep-brain stimulation for anorexia nervosa. World Neurosurg. 2013; 80(3-4):S29.e1-10.
20. Zesiewicz TA, Elble R, Louis ED, et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2005; 64(12):2008-2020.
21. Zesiewicz TA, Elble RJ, Louis RJ, et al. Evidence-based guideline update: Treatment of essential tremor report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2011; 77(19):1752-1755.
22. Zesiewicz TA, Sullivan KL, Arnulf I, et al. Practice parameter: treatment of nonmotor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010; 74(11):924-931.

Websites for Additional Information

1. American Association of Neurological Surgeons. Deep Brain Stimulation. 2007. Available at: http://www.aans.org/Patient%20Information/Conditions%20and%20Treatments/Deep%20Brain%20Stimulation.aspx. Accessed on November 7, 2022.
2. National Library of Medicine. Medical Encyclopedia: Parkinson disease. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000755.htm. Accessed on November 7, 2022.

Index

Parkinson Disease
Reclaim

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	09/27/2023	Updated Coding section with 10/01/2023 ICD-10-CM changes to add G20.A1-G20.C replacing G20; also added HCPCS code C1787.
Reviewed	11/10/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
Revised	11/11/2021	MPTAC review. Clarified MN statement regarding DBS for epilepsy. Added new MN criteria for DBS for obsessive-compulsive disorder. Updated Rationale, Coding and References sections.
Reviewed	11/05/2020	MPTAC review. Updated Scope, Rationale, and References sections. Updated Coding section with 01/01/2021 CPT changes; added 64999 replacing code 61870 which will be deleted 12/31/2020.
Revised	05/14/2020	MPTAC review. Clarified MN statement regarding primary dystonia. Added new MN criteria for DBS for epilepsy. Revised and clarified the INV and NMN statement regarding all other conditions. Updated Rationale, Coding and References sections.
Reviewed	02/20/2020	MPTAC review. Updated Rationale, References, and Websites sections.
Revised	03/21/2019	MPTAC review. Clarified first MN statement. Updated Rationale and References sections.
Revised	05/03/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Removed MN criteria requiring failure of prior VNS treatment before RNS system. Updated Rationale and References sections.
Reviewed	08/03/2017	MPTAC review. Updated formatting in Position Statement section. Updated Rationale and References sections.
Reviewed	08/04/2016	MPTAC review.
Reviewed	07/20/2016	Behavioral Health Subcommittee review. Updated Rationale and Reference sections.
	01/01/2016	Updated Coding section with 01/01/2016 HCPCS changes; removed ICD-9 codes.
Reviewed	08/06/2015	MPTAC review. Updated Rationale and Reference sections.
	01/01/2015	Updated Coding section with 01/01/2015 CPT changes; removed code 61875 deleted 12/31/2014.
Revised	08/14/2014	MPTAC review. Revised medically necessary criteria for cortical stimulation devices regarding the use of VNS. Updated Rationale section.
Revised	05/15/2014	MPTAC review. Revised document title to include cortical and cerebellar stimulation. Added medically necessary criteria for deep brain stimulation in

		individuals with incapacitating tremor from Parkinson's disease. Added new medically necessary and investigational and not medically necessary position statements addressing cortical stimulation. Updated Rationale, Coding and Reference sections.
	01/01/2014	Updated Coding section with 01/01/2014 HCPCS changes.
Reviewed	05/09/2013	MPTAC review. Rationale and Reference sections updated.
Reviewed	05/10/2012	MPTAC review. Rationale and References updated.
Reviewed	05/19/2011	MPTAC review. Rationale and References updated.
Revised	05/13/2010	MPTAC review. Clarified the position statement for medically necessary criteria. Added dystonia to investigational and not medically necessary statement regarding DBS for other causes. Rationale, Background, Definitions, Coding and References updated.
	08/27/2009	Added *Unified Parkinson's Disease Rating Scale (UPDRS)* to the definitions; updated bibliography.
Reviewed	05/21/2009	MPTAC review. Rationale, coding and references updated.
Reviewed	05/15/2008	MPTAC review. References updated.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review. References and Rationale updated. Coding updated; removed HCPCS E0752, E0754, E0756, E0757, and E0758 deleted 12/31/2005.
Reviewed	06/08/2006	MPTAC review. References and coding updated.
	01/01/2006	Updated coding section with 01/01/2006 CPT/HCPCS changes
	11/17/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	06/16/2003	SURG.00026	Electrical Stimulation – Deep Brain, Cerebellar
WellPoint Health Networks, Inc.	04/28/2005	3.10.01	Deep Brain Stimulation for Tremor