Medical Policy

BlueCross BlueShield of Kansas

An Independent Licensee of the
Blue Cross and Blue Shield Association.

Title: Deep Brain Stimulation

Professional
Original Effective Date: March 1, 1985
Revision Date(s): June1, 1986;
October 1, 1994; June 1, 1997;
July 1, 1998; June 1, 2006;
November 1, 2006; June 13, 2011;
September 17, 2013; February 10, 2015;
May 24, 2017; January 1, 2019
Current Effective Date: May 24, 2017

Institutional
Original Effective Date: April 1, 2007
Revision Date(s): June 13, 2011;
September 17, 2013; February 10, 2015;
May 24, 2017; January 1, 2019

Current Effective Date: May 24, 2017

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact **Blue Cross and Blue Shield of Kansas Customer Service**.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
Individuals: • With essential tremor or tremor in Parkinson disease	Interventions of interest are: • Deep brain stimulation of the thalamus	Comparators of interest are: • Pharmacologic therapy • Permanent neuroablative procedure (eg, thalamotomy, pallidotomy)	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With symptoms associated with Parkinson disease	Interventions of interest are: • Deep brain stimulation of the globus pallidus interna or subthalamic nucleus	Comparators of interest are: • Pharmacologic therapy • Physical and speech therapy	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Populations	Interventions	Comparators	Outcomes
Individuals: • With primary dystonia	Interventions of interest are: • Deep brain stimulation of the globus pallidus interna or subthalamic nucleus	Comparators of interest are: • Pharmacologic therapy • Permanent neuroablative procedure (eg, thalamotomy, pallidotomy)	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With tardive dyskinesia or tardive dystonia	Interventions of interest are: • Deep brain stimulation	Comparators of interest are: • Pharmacologic therapy	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With epilepsy	Interventions of interest are: • Deep brain stimulation	Comparators of interest are: • Pharmacologic therapy	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With multiple sclerosis	Interventions of interest are: • Deep brain stimulation	Comparators of interest are: • Pharmacologic therapy	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With Tourette syndrome	Interventions of interest are: • Deep brain stimulation	Comparators of interest are: • Pharmacologic therapy • Cognitive-behavioral therapy	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With cluster headaches or facial pain	Interventions of interest are: • Deep brain stimulation	Comparators of interest are: • Pharmacologic therapy • Botulinum toxin • Conservative therapy (eg, diet, exercise)	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With treatment-resistant depression	Interventions of interest are: • Deep brain stimulation	Comparators of interest are: • Pharmacologic therapy • Behavioral therapy • Psychotherapy	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With obsessive-compulsive disorder	Interventions of interest are: • Deep brain stimulation	Comparators of interest are: • Pharmacologic therapy • Behavioral therapy • Psychotherapy	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, or chronic pain	Interventions of interest are: • Deep brain stimulation	Comparators of interest are: • Pharmacologic therapy • Behavioral therapy • Psychotherapy	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity

DESCRIPTION

Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into a central nervous system nucleus (eg, hypothalamus, thalamus, globus pallidus, subthalamic nucleus). DBS is used as an alternative to permanent neuroablative procedures for control of essential tremor (ET) and Parkinson's disease (PD). DBS is also being evaluated for the treatment of a variety of other neurologic and psychiatric disorders.

Objective
The objective of this evidence review is to determine whether deep brain stimulation improves the net health outcome in patients with various conditions such as tremor, epilepsy, dystonia, and depression.

Background

DEEP BRAIN STIMULATION
Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into the brain (ie, hypothalamus, 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 patient returns for permanent subcutaneous surgical 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, use of bilateral stimulation using 2 electrode arrays has also been investigated in patients with bilateral, severe symptoms. After implantation, noninvasive programming of the neurostimulator can be adjusted to the patient's symptoms. This feature may be important for patients with Parkinson disease (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 adverse effects of neurostimulation, such as dysarthria, disequilibrium, or involuntary movements.

Essential Tremor and PD
DBS has been investigated as an alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy. DBS has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of essential tremor (ET) and tremor associated with PD. More recently, there has been research interest in the use of DBS of the globus pallidus or subthalamic nucleus as a treatment of other parkinsonian symptoms, such as rigidity, bradykinesia, and akinesia. Another common morbidity associated with PD is the occurrence of motor fluctuations, referred to as "on and off" phenomena, related to the maximum effectiveness of drugs (ie, "on" state) and the nadir response during drug troughs (ie, "off" state). In addition, levodopa, the most commonly used anti-Parkinson's drug, may be associated with disabling drug-induced dyskinesias. Therefore, the optimal pharmacologic treatment of PD may involve a balance between optimal effects on PD symptoms and the appearance of drug-induced dyskinesias. The effect of DBS on both PD symptoms and drug-induced dyskinesias has also been studied.

Primary and Secondary Dystonia
DBS has also been investigated in patients with primary and secondary dystonia, defined as a neurologic movement disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, contorted, and painful movements or postures. Dystonia can be classified according to age of onset, bodily distribution of symptoms, and cause. Age of onset can occur during childhood or during adulthood. Dystonia can affect certain portions of the body (focal dystonia and multifocal dystonia) or the entire body (generalized dystonia). Torticollis is an example of a focal dystonia. Primary dystonia is defined when dystonia is the only symptom unassociated with other pathology. 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. Secondary dystonia is a dystonia

brought on by an inciting event, such as a stroke, trauma, or drugs. Tardive dystonia is a form of drug-induced secondary dystonia.

Cluster Headaches

DBS has been investigated in patients with chronic cluster headaches. Cluster headaches occur as episodic attacks of severe pain lasting from 30 minutes to several hours. The pain is usually unilateral and localized to the eye, temple, forehead, and side of the face. Autonomic symptoms that occur with cluster headaches include ipsilateral facial sweating, flushing, tearing, and rhinorrhea. Cluster headaches occur primarily in men and have been classified as vascular headaches that have been associated with among other things, high blood pressure, smoking, alcohol use. However, the exact pathogenesis of cluster headaches is uncertain. Positron emission tomography (PET) scanning and magnetic resonance imaging (MRI) have shown the hypothalamic region may be important in the pathogenesis of cluster headaches. Alterations in hormonal or serotonergic function may also play a role. Treatment of cluster headaches includes pharmacologic interventions for acute episodes and prophylaxis, sphenopalatine ganglion (SPG) blockade, and surgical procedures such as percutaneous SPG radiofrequency rhizotomy, and gamma knife radiosurgery of the trigeminal nerve.

Neurologic and Psychiatric Disorders

The role of DBS in treatment of other treatment-resistant neurologic and psychiatric disorders, particularly epilepsy, Tourette syndrome, major depressive disorders, and obsessive-compulsive disorder is also being investigated. Ablative procedures are irreversible and, though they have been refined, remain controversial treatments for intractable illness. Interest has shifted to neuromodulation through DBS of nodes or targets within neural circuits involved in these disorders. Currently, a variety of target areas are being studied.

Regulatory Status

In 1997, the Activa® Tremor Control System (Medtronic) was cleared for marketing by the U.S. Food and Drug Administration (FDA) for deep brain stimulation. The Activa® Tremor Control System consists of an implantable neurostimulator, a deep brain stimulator lead, an extension that connects the lead to the power source, a console programmer, a software cartridge to set electrical parameters for simulation, and a patient control magnet, which allows the patient to turn the neurostimulator on and off, or change between high and low settings.

The original FDA-labeled indications for Activa® were limited to unilateral implantation of the device for the treatment of tremor, but, in 2002, FDA-labeled indications were expanded to include bilateral implantation as a treatment to decrease the symptoms of advanced Parkinson disease not controlled by medication. In 2003, the labeled indications were further expanded to include "…unilateral or bilateral stimulation of the internal globus pallidus or subthalamic nucleus to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above." This latter indication was cleared for marketing by FDA through the humanitarian device exemption (HDE) process. In 2017, the indications for Parkinson disease were modified to include "adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's Disease of at least 4 years' duration that are not adequately controlled with medication."

In 2009, the Reclaim® device (Medtronic), a deep brain stimulator device, was cleared for marketing by FDA through the HDE process for the treatment of severe obsessive compulsive disorder.

In 2014, the Brio Neurostimulation System (now called Infinity; St. Jude Medical Neuromodulation) was cleared for marketing by FDA for the treatment of Parkinsonian tremor.

In 2016, the St. Jude Medical's Infinity DBS device with directional leads was approved by FDA. The directional leads enable the clinician to "steer" current to different parts of the brain. This tailored treatment reduces side effects. The Infinity system can be linked to Apple's iPod Touch and iPad Mini.

In December 2017, a second system with directional leads, the Vercise Deep Brain Stimulation System (Boston Scientific), was approved by FDA. This system is to be used as an adjunctive therapy from reducing motor symptoms of moderate-to-advanced levodopa-responsive PD inadequately controlled with medication alone.

FDA product code: MHY.

POLICY

I.   Unilateral deep brain stimulation of the thalamus may be considered **medically necessary** in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease.

II.   Bilateral deep brain stimulation of the thalamus may be considered **medically necessary** in patients with disabling, medically unresponsive tremor in both upper limbs due to essential tremor or Parkinson disease.

III.   Unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus may be considered **medically necessary** in the following patients:

    A.   Those with Parkinson's disease with ALL of the following:
        1.   a good response to levodopa
            AND
        2.   motor complications not controlled by pharmacologic therapy
            AND
        3.   ONE of the following:
            a)   a minimal score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours
                OR
            b)   Parkinson disease for at least 4 years

    B.   Patients older than 7 years with chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis).

IV.   Deep brain stimulation is considered **experimental/investigational** for:

    A.   other movement disorders, including but not limited to tardive dyskinesia, multiple sclerosis, and post-traumatic dyskinesia
    B.   treatment of chronic cluster headaches
    C.   other psychiatric or neurologic disorders, including but not limited to epilepsy, Tourette syndrome, depression, obsessive-compulsive disorder, anorexia nervosa, alcohol addiction, Alzheimer disease, and chronic pain

Policy Guidelines

1.   Disabling, medically unresponsive tremor is defined as all of the following:
    a.   tremor causing significant limitation in daily activities
    b.   inadequate control by maximal dosage of medication for at least 3 months before implant
2.   Contraindications to deep brain stimulation include:
    a.   patients who are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker
    b.   patients who have medical conditions that require repeated magnetic resonance imaging (MRI)

  c. patients who have dementia that may interfere with the ability to cooperate
  d. patients who have had botulinum toxin injections within the last 6 months

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through February 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

ESSENTIAL TREMOR AND TREMOR IN PARKINSON DISEASE

Unilateral Stimulation of the Thalamus

This section was informed by a TEC Assessment (1997) that focused on unilateral deep brain stimulation (DBS) of the thalamus as a treatment of tremor.[1] The Assessment concluded:

- Tremor suppression was total or clinically significant in 82% to 91% of operated sides in 179 patients who underwent implantation of thalamic stimulation devices. Results were durable for up to 8 years, and adverse events of stimulation were reported as mild and largely reversible.
- These results were at least as good as those associated with thalamotomy. An additional benefit of DBS is that recurrence of tremor may be managed by changes in stimulation parameters.

Studies identified in subsequent literature searches have supported the conclusions of the TEC Assessment. For example, Schuurman et al (2008) reported on 5-year follow-up of 68 patients comparing thalamic stimulation with thalamotomy for treatment of tremor due to Parkinson disease (PD; 45 patients), essential tremor (ET; 13 patients), and multiple sclerosis (MS; 10 patients).[2] Forty-eight (71%) patients were assessed at 5 years: 32 with PD, 10 with ET, and 6 with MS. The Frenchay Activities Index (FAI), the primary study outcome measure, was used to assess change in functional status; secondary measures included tremor severity, complication frequency, and patient-assessed outcomes. The mean difference (MD) between interventions, as measured on the FAI, favored thalamic stimulation at all time points: 4.4 (95% confidence interval

[CI], 1.1 to 7.7) at 6 months, 3.3 (95% CI, -0.03 to 6.6) at 2 years, and 4.0 (95% CI, 0.3 to 7.7) at 5 years. The procedures had similar efficacy for suppressing tremors. The effect of thalamic stimulation diminished in half of the patients with ET and MS. Neurologic adverse effects were higher after thalamotomy. Subjective assessments favored stimulation.

Hariz et al (2008) evaluated outcomes of thalamic DBS in patients with tremor-predominant PD who participated in a multicenter European study; the authors reported that, at 6 years postsurgery, tremor was still effectively controlled and appendicular rigidity and akinesia remained stable compared with baseline.[3]

Bilateral Stimulation of the Thalamus
Putzke et al (2005) reported on a series of 25 patients with ET treated with bilateral DBS for management of midline tremor (head, voice, tongue, trunk).[4] Three patients died of unrelated causes, 1 patient was lost to follow-up due to transfer of care, and 1 patient did not have baseline evaluation; these patients were not included in the analysis. Patients were evaluated at baseline (before implantation of second stimulator), and at 1, 3, 6, 12, 24, and 36 months. At 12 months, evaluations were obtained from 76% of patients; at 36 months, 50% of patients were evaluated. The most consistent improvement on the Tremor Rating Scale during both unilateral and bilateral stimulation was found for head and voice tremor. The incremental improvement over unilateral stimulation through the first 12 months of bilateral stimulation was significant (p<0.01). For bilateral stimulation at months 3 and 12, outcome measures were significantly better than unilateral stimulation at month 3 (p<0.05). Small sample size limited analysis at months 24 and 36. Dysarthria was reported in 6 (27%) patients and disequilibrium in 5 (22%) patients after bilateral stimulation in staged implantations. No patient reported dysarthria and 2 reported disequilibrium before bilateral stimulation.

Pahwa et al (2006) reported on long-term follow-up of 45 patients who underwent thalamic DBS, 26 of whom had ET; of these patients, 18 had unilateral and 8 had bilateral implantation.[5] Sixteen patients with unilateral and 7 with bilateral stimulators completed at least part of the 5-year follow-up evaluations. Patients with bilateral stimulation had a 78% improvement in mean motor tremor scores in the stimulation on state compared with baseline at 5-year follow-up (p=0.02) and 36% improvement in activities of daily living (ADL) scores. Patients with unilateral stimulation improved by 46% on motor tremor scores and 51% on ADL scores (p<0.01). Stimulation-related adverse events were reported in more than 10% of patients with unilateral and bilateral thalamic stimulators. Most were mild and were reduced with changes in stimulation parameters. Adverse events in patients with bilateral stimulation (eg, dysarthria and other speech difficulties, disequilibrium or balance difficulties, abnormal gait) persisted, despite optimization of the stimulation parameters.

Directional Deep Brain Stimulation
Two new DBS systems with directional leads are currently available (approved by the Food and Drug Administration [FDA] in 2016 and 2017). Directional leads potentially enable clinicians to target more specific areas of the brain to be treated with the direct current. Published evidence consists of several small observational studies, with sample sizes ranging from 7 to 13.[6-9] The studies showed that patients experienced improved tremor scores and improved quality of life (QOL). Compared with historical data from conventional DBS systems, directional DBS widened the therapeutic window and achieved beneficial effects using lower current level. Comparative, larger studies are needed to support the conclusions from these small studies. Data from a large study of 292 patients are expected in 2018.

Section Summary: Essential Tremor and Tremor in Parkinson Disease
A TEC Assessment concluded there was sufficient evidence that DBS of the thalamus results in clinically significant tremor suppression and that outcomes after DBS were at least as good as thalamotomy. Subsequent studies reporting long-term follow-up have supported the conclusions of the TEC Assessment and found that tremors were effectively controlled 5 to 6 years after DBS. A new technology in DBS systems, using directional leads, has recently emerged and data evaluating the new technology is expected to be published in 2018.

SYMPTOMS ASSOCIATED WITH PD
Advanced PD
Stimulation of the Internal Segment of the Globus Pallidus Interna and Subthalamic Nucleus
This section was informed by a TEC Assessment (2001) that focused on the use of DBS of the internal segment of the globus pallidus interna (GPi) and subthalamic nucleus (STN) for a broader range of PD symptoms.[10] The Assessment concluded:

- A wide variety of studies have consistently demonstrated that DBS of the GPi or STN results in significant improvements, as measured by standardized rating scales of neurologic function. The most frequently observed improvements consist of increased waking hours spent in a state of mobility without dyskinesia, improved motor function during "off" periods when levodopa is not effective, reduction in frequency and severity of levodopa-induced dyskinesia during periods when levodopa is working ("on" periods), improvement in cardinal symptoms of PD during periods when medication is not working, and, in the case of bilateral DBS of the STN, reduction in the required daily dosage of levodopa and/or its equivalents. The magnitude of these changes were both statistically significant and clinically meaningful.
- The beneficial treatment effect lasted at least for the 6 to 12 months observed in most trials. While there was not a great deal of long-term follow-up, the available data were generally positive.
- Adverse effects and morbidity were similar to those known to occur with thalamic stimulation.
- DBS possesses advantages to other treatment options. Compared with pallidotomy, DBS can be performed bilaterally. The procedure is nonablative and reversible.

A systematic review of RCTs by Perestelo-Perez et al (2014) compared the impact of DBS plus medication with medication alone (or plus sham DBS) on PD outcomes.[11] Six RCTs (total N=1184 patients) were included in the review. Five trials exclusively involved bilateral stimulation to the STN and, in the sixth trial, half of the patients received stimulation to the STN and the other half had stimulation to the GPi. Motor function assessment was blinded in 2 trials and the randomization method was described in 4 trials. Five studies reported motor function, measured by the Unified Parkinson's Disease Rating Scale–III (UPDRS). In the off-medication phase, motor function was significantly higher with DBS than with control (weighted mean difference [WMD], 15.20; 95% CI, 12.23 to 18.18; standard mean difference [SMD], 1.35). In the on-medication phase, there was also significantly greater motor function with DBS than with control (WMD=4.36; 95% CI, 2.80 to 5.92; SMD=0.53). Meta-analyses of other outcomes (eg, ADLs, QOL, dementia, depression) also favored the DBS group.

An earlier systematic review by Kleiner-Fisman et al (2006) included both RCTs and observational studies; reviewers examined the literature on subthalamic stimulation for patients with PD who had failed medical management.[12] Twenty studies, primarily uncontrolled cohorts or case series, were included in the meta-analysis. Subthalamic stimulation was found to improve ADLs by 50%

over baseline, as measured by the UPDRS-II (decrease of 13.35 points out of 52). There was a 28-point decrease in the UPDRS-III score (out of 108), indicating a 52% reduction in the severity of motor symptoms that occurred while the patient was not taking medication. A strong relation was found between the preoperative dose response to levodopa and improvements in both the UPDRS-II and -III scores. The analysis found a 56% reduction in medication use, a 69% reduction in dyskinesia, and a 35% improvement in QOL with subthalamic stimulation.

A meta-analysis by Appleby et al (2007) found that the rate of suicidal ideation and suicide attempts associated with DBS for PD ranged from 0.3% to 0.7%.[13] The completed suicide rate ranged from 0.16% to 0.32%. In light of the rate of suicide in patients treated with DBS, reviewers argued for prescreening for suicide risk.

PD With Early Motor Complications
Schuepbach et al (2013) published an RCT evaluating DBS in patients with PD and early motor complications.[14] Key eligibility criteria included age 18 to 60 years, disease duration of at least 4 years, improvement of motor signs of at least 50% with dopaminergic medication, and PD disease severity below stage 3 in the on-medication condition. A total of 251 patients enrolled, 124 of whom were assigned to DBS plus medical therapy and 127 to medical therapy alone. Analysis was intention to treat and blinded outcome assessment was done at baseline and 2 years.

The primary end point was mean change from baseline to 2 years in the summary index of the Parkinson Disease Questionnaire (PDQ-39), which has a maximum score of 39 points, with higher scores indicating higher QOL. Mean baseline scores on the PDQ-39 were 30.2 in the DBS plus medical therapy group and 30.2 in the medical therapy only group. At 2 years, the mean score increased by 7.8 points in the DBS plus medical therapy group and decreased by 0.2 points in the medical therapy only group (mean change between groups, 8.0; p=0.002). There were also significant between-group differences in major secondary outcomes, favoring the DBS plus medical therapy group (p<0.01 on each): severity of motor signs, ADLs, severity of treatment-related complications, and the number of hours with good mobility and no troublesome dyskinesia. The first 3 secondary outcomes were assessed using UPDRS subscales. Regarding medication use, the levodopa-equivalent daily dose was reduced by 39% in the DBS plus medical therapy group and increased by 21% in the medical therapy only group.

Sixty-eight patients in the DBS plus medical therapy group and 56 in the medical therapy only group experienced at least 1 serious adverse event. This included 26 serious adverse events in the DBS group that were surgery- or device-related; reoperation was necessary in 4 patients.

GPi vs STN Stimulation
A number of meta-analyses have compared the efficacy of GPi with STN stimulation in PD patients.[15-20] The meta-analysis by Tan et al (2016) included only RCTs comparing the 2 types of stimulation in patients with advanced PD and considered a range of outcomes.[17] This review included RCTs evaluating patients with PD who were responsive to levodopa, had at least 6 months of follow-up, and reported at least one of the following outcome measures: UPDRS-III, Beck Depression Inventory–II (BDI), levodopa-adjusted dose, neurocognitive status, or QOL.[17] Ten RCTs met eligibility criteria and were included in the quantitative synthesis. After 6 months, there were no significant differences in the UPDRS-III scores between the GPi and STN groups for patients in the off-medication/on-simulation state (5 studies; MD = -1.39; 95% CI, -3.70 to 0.92) or the on-medication/on-stimulation state (5 studies; MD = -0.37; 95% CI, -2.48 to 1.73). At the 12- and 24-month follow-ups, only 1 to 3 studies reported data on the UPDRS-III score. In a pooled analysis of the levodopa-adjusted dose, there was a significant difference between the GPi and STN groups, favoring STN (6 studies; MD=0.60; 95% CI, 0.46 to 0.74). However, the analysis

of BDI-II scores favored the GPI group (4 studies; MD = -0.31; 95% CI, -0.51 to -0.12). Other meta-analyses had similar mixed findings and none concluded that 1 type of stimulation was clearly better than the other for patients with advanced PD.

Section Summary: Symptoms Associated With PD
A number of RCTs and systematic reviews of the literature have been published. A TEC Assessment concluded that studies evaluating DBS of the GPi or STN have consistently demonstrated clinically significant improvements in outcomes (eg, neurologic function). Other systematic reviews have also found significantly better outcomes after DBS than after a control intervention. One RCT compared DBS plus medical therapy with medical therapy alone in patients with levodopa-responsive PD of at least 4 years in duration and uncontrolled motor symptoms. The trial found that QOL at 2 years (eg, motor disability, motor complications) was significantly higher when DBS was added to medical therapy. Meta-analyses of RCTs comparing GPi and STN have had inconsistent findings and did not conclude that 1 type of stimulation was clearly superior to the other.

PRIMARY DYSTONIA
DBS for the treatment of primary dystonia received FDA approval through the humanitarian device exemption process in 2003. The humanitarian device exemption approval process is available for conditions that affect fewer than 4000 Americans per year. According to this approval process, the manufacturer is not required to provide definitive evidence of efficacy, but only probable benefit. The approval was based on the results of DBS in 201 patients represented in 34 manuscripts.[21] Three studies reported at least 10 cases of primary dystonia. In these studies, clinical improvement with DBS ranged from 50% to 88%. A total of 21 pediatric patients were studied; 81% were older than age 7 years. Among these patients, there was a 60% improvement in clinical scores. As noted in the analysis of risk and probable benefit, the only other treatment options for chronic refractory primary dystonia are neurodestructive procedures. DBS provides a reversible alternative.

Moro et al (2017) published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia).[22] Reviewers included studies with at least 10 cases. Fifty-eight articles corresponding to 54 unique studies were identified; most involved bilateral DBS of the GPi. There were only 2 controlled studies, 1 RCT (Volkmann et al [2014]; described below) and 1 study that included a double-blind evaluation with and without stimulation. Twenty-four studies reported data using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and were included in a meta-analysis. These studies enrolled a total of 523 patients (mean per study, 22 patients) and had a mean follow-up of 32.3 months (range, 6-72 months). In a pooled analysis of BFMDRS motor scores (scale range, 0-120; higher scores indicate more severe dystonia) from 24 studies, the mean increase in scores at 6 months compared with baseline was 23.8 points (95% CI, 18.5 to 29.1 points). The mean increase in the motor score at last follow-up compared with baseline was 26.6 points (95% CI, 22.4 to 30.9 points). The mean percentage improvement was 59% at 6 months and 65% at last follow-up. Fourteen studies reported BFMDRS disability scores (scale range, 0-30). Compared with baseline, the mean absolute change in the score was 4.8 points (95% CI, 3.1 to 6.6 points) at 6 months and 6.4 points (95% CI, 5.0 to 7.8 points) at last follow-up. The mean percentage improvement was 44% at 6 months and 59% at last follow-up.

The RCT, which was an industry-sponsored, patient- and observer-blinded evaluation of pallidal neurostimulation in subjects with refractory cervical dystonia, was published by Volkmann et al (2014).[23] The trial included 62 adults with cervical dystonia for 3 or more years in duration, a

severity score of 15 or more on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), and an unsatisfactory response to botulinum toxin injection and oral medication. Patients were randomized to DBS (n=32) or to sham stimulation (n=30). The primary outcome was change in the TWSTRS severity score at the end of the blinded study period (3 months); thereafter, all patients received open-label active stimulation. After 3 months, mean TWSTRS score improved by 5.1 points (95% CI, 3.5 to 7.0 points) in the neurostimulation group and by 1.3 points (95% CI, 0.4 to 2.2 points) in the sham group. The between-group difference was 3.8 points (95% CI, 1.8 to 5.8 points; p=0.024). Findings were mixed on the prespecified secondary outcomes. There was significantly greater improvement in the neurostimulation group than in the sham group on the TWSTRS disability score and the Bain Tremor Scale score, but not on the TWSTRS pain score or the Craniocervical Dystonia Questionnaire–24 score. During the 3-month blinded study period, 22 adverse events were reported in 20 (63%) patients in the neurostimulation group and 13 adverse events were reported in 12 (40%) patients in the sham group. Of these 35 adverse events, 11 (31%) were serious. Additionally, 40 adverse events, 5 of which were serious, occurred during 9 months of the open-label extension period. During the study, 7 patients experienced dysarthria (ie, slightly slurred speech), which was not reversible in 6 patients.

Section Summary: Primary Dystonia

A review prepared for FDA and a 2017 systematic review have evaluated evidence on DBS for primary dystonia. There are numerous small case series and an RCT. The RCT found that severity scores improved more after active than after sham stimulation. A pooled analysis of 24 studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months).

TARDIVE DYSKINESIA AND TARDIVE DYSTONIA

Stimulation of the GPi was examined as a treatment for tardive dyskinesia in a multicenter case series by Damier et al (2007), with a double-blind evaluation at 6 months (comparison of symptoms in the on and off positions).[24] The trial was stopped early due to successful treatment (>40% improvement at 6 months) in the first 10 patients. In the double-blind evaluation of these patients, stimulation was associated with a mean decrease of 50% in the symptom score when the device was on vs off.

Outcomes on motor function, QOL, and mood in a series of 9 patients treated with DBS of the GPi for tardive dystonia were reported by Gruber et al (2009).[25] One week and 3 to 6 months after surgery, BFMDRS motor scores were improved by 56.4% and 74.1%, BFMDRS disability scores by 62.5% and 88.9%, and Abnormal Involuntary Movement Scale (AIMS) scores by 52.3% and 69.5%, respectively. At last follow-up (mean, 41 months; range, 18-90 months), BFMDRS motor scores were reduced compared with presurgical assessment by 83%, BFMDRS disability score by 67.7%, and AIMS scores by 78.7%.

Pouclet-Courtemanche et al (2016) reported on a case series of 19 patients with severe pharmaco-resistant tardive dyskinesia treated with DBS.[26] Patients were assessed after 3, 6, and 12 months after the procedure. At 6 months, all patients had experienced greater than 40% reduction in symptoms as measured on the Extrapyramidal Symptoms Rating Scale (ESRS). At 12 months, the mean decrease in ESRS score was 58% (range, 21%-81%).

Section Summary: Tardive Dyskinesia and Tardive Dystonia

Evidence for the use of DBS to treat tardive syndromes consists of case series. One study of DBS in patients with tardive dyskinesia included a double-blind evaluation of DBS at 6 months.

Symptoms decreased more with the device turned on but the study was small (10 patients were evaluated) and included only patients with DBS for 6 months. Two subsequent case series included 9 and 19 patients, respectively, and reported favorable results with DBS treatment. Additional studies evaluating more patients, especially RCTs or other controlled studies, are needed to provide greater certainty concerning the efficacy of DBS for this population.

EPILEPSY
Systematic Reviews
Two systematic reviews on the use of DBS for drug-resistant epilepsy, both published in 2018, assessed many of the same studies.[27,28] The larger review, by Li et al (2018), identified 10 RCTs and 48 uncontrolled studies.[27] The literature search date was not reported. Meta-analyses were not performed. Summaries of the studies were discussed by area of the brain targeted by DBS. A review of the studies showed that DBS might be effective in reducing seizures when DBS targets the anterior nucleus of the thalamus or the hippocampus. Across studies, more than 70% of patients experienced a reduction in seizures by 50% or more. However, there were very few RCTs and the observational studies had small sample sizes. Individual responses varied, depending on seizure syndrome, presence or absence of structural abnormalities, and electrode position. Results were inconclusive when DBS targeted the centromedian nucleus of the thalamus, the cerebellum, and the subthalamic nuclei. Safety data on DBS were limited due to the small population sizes. The RCT in which DBS targeted the anterior nucleus of the thalamus (Fisher et al [2010][29] described below) reported paresthesias (23%), implant site pain (21%), and implant site infection (13%). Reviewers concluded that more robust clinical trials would be needed.

Randomized Controlled Trials
Fisher et al (2010) conducted a U.S. multicenter, double-blind, randomized trial, Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy (SANTE) (see Table 1).[29] Included were 110 patients, ages 18 to 65 years, who experienced at least 6 partial seizures (including secondarily generalized seizures) per month, but no more than 10 per day. (An additional 47 patients were enrolled in the trial but did not undergo implantation.) At least 3 antiepileptic drugs must have failed to produce adequate seizure control before baseline, with 1 to 4 antiepileptic drugs used at the time of study entry. Patients were asked to keep a daily seizure diary during treatment. All patients received DBS device implantation, with half the patients randomized to stimulation (n=54) and half to no stimulation (n=55) during a 3-month blinded phase; thereafter all patients received unblinded stimulation. Baseline monthly median seizure frequency was 19.5. During the first and second months of the blinded phase, the difference in seizure reduction between stimulation on (-42.1%) and stimulation off (-28.7%) did not differ significantly. In the last month of the blinded phase, the stimulated group had a significantly greater reduction in seizures (-40.4%) than the control group (-14.5%; p=0.002; see Table 2).

Troster et al (2017) assessed neuropsychological adverse events from the SANTE trial during the 3-month blinded phase, and at 7-year follow-up during the open-label noncomparative phase (see Table 2).[30] At baseline, there were no differences in depression history between groups. During the 3-month blinded phase of the trial, depression was reported in 8 (15%) patients from the stimulation group and in 1 (2%) patient from the no stimulation group (p=0.02). At 7-year follow-up, after the treatment groups had been combined, there was no statistically significant difference in Profile of Mood State depression score compared with baseline. Memory adverse events also occurred at significantly different rates between the treatment groups during the blinded phase (7 in the active group, 1 in the control group; p=0.03). At 7-year follow-up, most cognitive function tests did not improve over baseline measurements.

Cukiert et al (2017) conducted a double-blind, placebo-controlled randomized trial evaluating 16 patients with refractory temporal lobe epilepsy (see Table 1).[31] All patients underwent DBS device implantation, and were followed for 6 months. Patients were seen weekly to receive the treatment or placebo. To maintain double-blind status, programming was performed by a nontreating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last 2 months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. Results are summarized in Table 2.

Table 1. Summary of RCT Characteristics for Epilepsy

Study	Country	Sites	Dates	Participants	Interventions	
					Active	Comparator
Fisher et al (2010)[29]; Troster et al (2017)[30]	U.S.	17	NR	Patients with partial seizures, including secondary generalized seizures, refractory to ≥3 medications	5-V stimulus intensity (n=54)	No stimulation (n=55)
Cukiert et al (2017)[31]	Brazil	1	2014-2016	Patients with temporal lobe epilepsy, refractory to ≥3 medications	Weekly 0.4-V to 2-V stimulus intensity (n=8)	Weekly impedance testing, no stimulation (n=8)

NR: not reported; RCT: randomized controlled trial; V: volts.

Table 2. Summary of RCT Outcomes for Epilepsy

Study	Seizure Reduction, % (p)			Adverse Events
	1 Month	2 Months	3 Months	
Fisher et al (2010)[29]; Troster et al (2017)[30]				
Between-group difference	-11% (*NS*)	-11% (*NS*)	-29% (0.002)	3 months: higher rate of depression and memory adverse events in treatment group (difference disappeared in long-term follow-up)
	FIAS at 6 Months			
Cukiert et al (2017)[31]				
Stimulation on	4 seizure-free; 3 responders; 1 no response			2 patients with local skin erosions at cranial site of implant, treated with antibiotics
Stimulation off	0 seizure-free; 3 responders; 5 no response			

FIAS: focal impaired awareness seizure; RCT: randomized controlled trial.

Observational Studies

Long-term outcomes of the SANTE trial were reported by Salanova et al (2015).[32] The uncontrolled open-label portion of the trial began after 3 months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician's discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the 3-year follow-up, and 83 (75%) completed 5 years. Among patients with at least 70 days of diary entries, the median change in seizure frequency from baseline was 41% at 1 year and 69% at 5 years (p<0.001 for both). During the trial, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first months after implantation. They included implant-site infection (10%

of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the trial and none was considered to be device-related. Depression was reported in 41 (37%) patients following implant; in 3 cases, it was considered device-related. Memory impairment (nonserious) was reported in 30 (27%) patients during the trial, half of whom had a history of the condition. Although some patients appeared to benefit from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the trial, while significant, was modest overall.

Kim et al (2017) conducted a retrospective chart review of 29 patients with refractory epilepsy treated with DBS.[33] Patients' mean age was 31 years, they had had epilepsy for a mean of 19 years, and had a mean preoperative frequency of tonic-clonic seizures of 27 per month. Mean follow-up was 6.3 years. Median seizure reduction from baseline was 71% at year 1, 74% at year 2, and ranged from 62% to 80% through 11 years of follow-up. Complications included 1 symptomatic intracranial hemorrhage, 1 infection requiring removal and reimplantation, and 2 lead disconnections.

Section Summary: Epilepsy
A systematic review identified several RCTs and many observational studies in which DBS was evaluated for the treatment of epilepsy. The largest RCT consisted of a 3-month blinded phase in which patients were randomized to stimulation or no stimulation. After the randomized phase, all patients received stimulation and were followed for 13 additional months. Findings in the first 3 months were mixed: patients reported significantly fewer seizures in the third month, but not in the first or second month. In the uncontrolled follow-up period of the RCT and in many small observational studies, patients reported fewer seizures compared with baseline, however, without a control group, interpretation of results is limited. Adverse events, including device-related serious adverse events were reported in about one-third of patients. The risk-benefit ratio is uncertain.

MULTIPLE SCLEROSIS
Schuurman et al (2008) reported on 5-year follow-up for 68 patients in a study that compared thalamic stimulation with thalamotomy for multiple indications, including 10 patients with MS.[2] Trial details are discussed with essential tremor in the section on Unilateral Stimulation of the Thalamus. The small numbers of patients with MS in this trial limits conclusions that can be drawn.

Section Summary: Multiple Sclerosis
One RCT reporting on 10 MS patients provides insufficient data for drawing conclusions on the efficacy of DBS for this population.

TOURETTE SYNDROME
Several systematic reviews of the literature on DBS for Tourette syndrome have been published.[34-37] Most recent systematic reviews (ie, those published in 2015-2017) qualitatively described the literature. Only Baldermann et al (2016) conducted pooled analyses of study data.[34] That review identified 57 studies on DBS for Tourette syndrome, four of which were randomized crossover studies. The studies included a total of 156 cases. Twenty-four studies included a single patient and 4 had sample sizes of 10 or more (maximum, 18 patients). Half of the patients (n=78) received thalamus stimulation and the next most common areas of stimulation were the GPi anteromedial part (n=44) and post ventrolateral part (n=20). Two of the RCTs used thalamic stimulation, one used bilateral globus pallidus stimulation, and one used both. The primary outcome was the Yale Global Tic Severity Scale (YGTSS). In a pooled analysis of within-subject pre-post data, there was a median improvement of 53% in YGTSS score, a decline from a median score of 83 to 35 at last follow-up. Moreover, 81% of patients showed at least a 25% reduction in

YGTSS score and 54% showed improvements of 50% or more. In addition, data were pooled from the 4 crossover RCTs: 27 patients received DBS and 27 received a control intervention. Targets included the thalamus and the globus pallidus. In the pooled analysis, there was a statistically significant between-group difference, favoring DBS (SMD=0.96; 95% CI, 0.36 to 1.56). Reviewers noted that the effect size of 0.96 would be considered be large.

A systematic review by Piedad et al (2012) examined patient and target selection for use of DBS for subjects with Tourette syndrome.[38] Most clinical trials evaluating DBS for Tourette syndrome have targeted the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus. Other targets investigated have included the STN, caudate nucleus, GPi, and the anterior limb of the internal capsule and nucleus accumbens. Reviewers found no clear consensus in the literature for which patients should be treated and what the best target is.

The crossover RCT with the largest sample size was published by Kefalopoulou et al (2015).[39] The double-blind trial included 15 patients with severe medically refractory Tourette syndrome; all received bilateral GPi surgery for DBS and were randomized to the off-stimulation phase first or the on-stimulation phase first for 3 months, followed by the opposite phase for the next 3 months. Of the 15 receiving surgery, 14 were randomized and 13 completed assessments after both on and off phases. For the 13 trial completers, mean YGTSS scores were 80.7 in the off-stimulation phase and 68.3 in the on-stimulation phase. The mean difference in YGTSS scores indicated an improvement of 12.4 points (95% CI, 0.1 to 24.7 points), which was statistically significant (p=0.048) after Bonferroni correction. There was no significant between-group difference in YGTSS scores for patients randomized to the on-stimulation phase first or second. Three serious adverse events were reported, 2 related to surgery and 1 related to stimulation. Reviewers noted that the most effective target of the brain for DBS in patients with Tourette syndrome needs additional study.

Section Summary: Tourette Syndrome
A number of uncontrolled studies,4 crossover RCTs, and several systematic reviews have been published. Most studies, including the RCTs, had small sample sizes (ie, ≤15 patients) and used a variety of DBS targets. A 2015 meta-analysis suggested that DBS might improve outcomes in patients with Tourette syndrome. However, the optimal target for DBS is not known and additional controlled studies in larger numbers of patients are needed.

CLUSTER HEADACHE AND FACIAL PAIN
DBS of the posterior hypothalamus for the treatment of chronic cluster headaches has been investigated, because functional studies have suggested cluster headaches have a central hypothalamic pathogenesis.

Fontaine et al (2010) published the results of a prospective crossover, double-blind, multicenter trial in 11 patients who received DBS of the posterior hypothalamus for severe refractory chronic cluster headache.[40] The randomized phase compared active with sham stimulation during 1-month periods and was followed by a 1-year open phase. Severity of cluster headache was assessed using the weekly attack frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact, and QOL (12-Item Short-Form Health Survey). During the randomized phase, no significant changes in primary or secondary outcome measures were observed between active and sham stimulation. At the end of the open phase, 6 of 11 patients reported greater than 50% reduction in the weekly frequency of attacks.

Another research group from Europe published 2 case series (potentially overlapping) on use of DBS for the ipsilateral posterior hypothalamus in patients with chronic cluster headache.[41,42] Stimulation was reported to result in long-term pain relief (1-26 months of follow-up) without significant adverse events in 16 patients with chronic cluster headaches and in 1 patient with neuralgiform headache; treatment failed in the 3 patients who had atypical facial pain.

Section Summary: Cluster Headache and Facial Pain
Several case series and a crossover RCT have been published on use of DBS for cluster headache or facial pain. The RCT included 11 patients; there were no significant differences between groups receiving active and sham stimulation. Additional RCTs or controlled studies are needed.

TREATMENT-RESISTANT DEPRESSION
Systematic Reviews
A variety of target areas are being investigated for use of DBS for treatment-resistant depression. A systematic review by Morishita et al (2014) identified 22 published reports with 6 different approaches or targets, including the nucleus accumbens, ventral capsule/ventral striatum, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle.[43] Only 3 identified studies were controlled with sham stimulation periods, and 2 multicenter RCTs evaluating subgenual cingulate cortex and ventral striatum/ventral capsule DBS were terminated due to futility (interim analysis demonstrating very low probability of success if the trial was completed as planned). A systematic review by Mosley et al (2015) identified an RCT on DBS for depression[44]; this trial is described next.

Randomized Controlled Trials
An industry-sponsored, double-blind RCT evaluating DBS targeting the ventral capsule/ventral striatum in patients with chronic treatment-resistant depression was published by Dougherty et al (2015).[45] The trial included 30 patients with a major depressive episode lasting at least 2 years and inadequate response to at least 4 trials of antidepressant therapy. Participants were randomized to 16 weeks of active (n=16) or to sham (n=14) DBS, followed by an open-label continuation phase. One patient, who was assigned to active treatment, dropped out during the blinded treatment phase. The primary outcome was clinical response at 16 weeks, defined as 50% or more improvement from baseline on Montgomery-Asberg Depression Rating Scale (MADRS) score. A response was identified in 3 (20%) of 15 patients in the active treatment group and in 2 (14%) of 14 patients in the sham control group (p=0.53). During the blinded treatment phase, psychiatric adverse events occurring more frequently in the active treatment group included worsening depression, insomnia, irritability, suicidal ideation, hypomania, disinhibition, and mania. Psychiatric adverse events occurring more frequently in the sham control group were early morning awakening and purging. Findings of this trial did not support a conclusion that DBS is effective for treating treatment-resistant depression.

A crossover RCT evaluating active and sham phases of DBS stimulation in 25 patients with treatment-resistant depression was published after the systematic review by Bergfeld et al (2016).[46] Prior to the randomized phase, all patients received 52 weeks of open-label DBS treatment with optimization of settings. Optimization ended when patients achieved a stable response of at least 4 weeks or after the 52-week period ended. At the end of the open-label phase, 10 (40%) patients were classified as responders (≥50% decrease in the Hamilton Depression Rating Scale [HAM-D] score) and 15 (60%) patients were classified as nonresponders. After the 52 weeks of open-label treatment, patients underwent 6 weeks of double-blind active and sham stimulation. Sixteen (64%) of 25 enrolled patients participated in the randomized phase (9 responders, 7 nonresponders). Nine patients were prematurely crossed over to the other

intervention. Among all 16 randomized patients, HAM-D scores were significantly improved at the end of the active stimulation phase (mean HAM-D score, 16.5) compared with the sham stimulation phase (mean HAM-D score, 23.1; p<0.001). Mean HAM-D scores were similar after the active (19.0) and sham phases for initial nonresponders (23.0). Among initial responders, the mean HAM-D score was 9.4 after active stimulation and 23 after sham stimulation. Trial limitations included the small number of patients in the randomized phase and potential bias from having an initial year of open-label treatment; patients who had already responded to DBS over a year of treatment were those likely to respond to active than sham stimulation in the double-blind randomized phase; and findings might not be generalizable to patients with treatment-resistant depression who are DBS-naive.

Section Summary: Treatment-Resistant Depression
A number of case series and several RCTs evaluating DBS in patients with treatment-resistant depression have been published. Two RCTs were terminated for futility. Another RCT did not find a statistically significant difference between groups in the primary outcome (clinical response) and adverse psychiatric events occurred more frequently in the treatment group than in the control group. More recently, a controlled crossover trial randomized patients to active or to sham stimulation after a year of open-label stimulation. There was a greater reduction in symptom scores after active stimulation, but only in patients who were responders in the open-label phase; these findings might not be generalizable.

OBSESSIVE-COMPULSIVE DISORDER
Several systematic reviews evaluating DBS for obsessive-compulsive disorder (OCD) have been published.[47-51] Two of these reviews included meta-analyses and pooled study findings. Kisely et al (2014) included only double-blind RCTs of active vs sham DBS.[50] Five trials (total N=50 patients) met eligibility criteria and data on 44 patients were available for meta-analysis. Three were parallel-group RCTs with or without a crossover phase and 2 were only crossover trials. The site of stimulation was the anterior limb of the internal capsule (3 studies), the nucleus accumbens (1 study), and the STN (1 study). Duration of treatment ranged from 2 to 12 weeks. All studies reported scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which is a 10-item clinician-rated scale, in which higher ratings reflect more intense symptoms, and a score of 24 or more (of a possible 40) indicates severe illness. Most studies designate a therapeutic response as a reduction in Y-BOCS score of 35% or more from the pretreatment baseline, with a reduction of 25% to 35% considered a partial response. Only 1 of the 5 studies compared the proportion of responders on the Y-BOCS as an outcome measure and that study did not find a statistically significant difference between active and sham stimulation groups. All studies reported the outcome measure, mean reduction in Y-BOCS score. When data from the 5 studies were pooled, there was a statistically significant reduction in the mean Y-BOCS in the active vs the sham group (MD = -8.49; 95% CI, -12.18 to -4.80). The outcome measure, however, does not permit conclusions on whether the between-group difference is clinically meaningful. Trial authors reported 16 serious adverse events including 1 cerebral hemorrhage and 2 infections requiring electrode removal. Additionally, nonserious transient adverse events were reported, including 13 reports of hypomania, 6 of increase in depressive or anxious symptoms, and 6 of headaches.

A meta-analysis by Alonso et al (2015) included studies of any type (including case reports) evaluating DBS for OCD and reporting changes in Y-BOCS score.[49] Reviewers identified 31 studies (total N=116 patients). They did not report study type (ie, controlled vs uncontrolled); however, the meta-analysis only included patients who received active treatment. Twenty-four (77%) studies included 10 or fewer patients. Most studies (24, including 83 patients) involved DBS of striatal areas. Of the remaining studies, 5 (27 patients) addressed STN stimulation and 2 (6

patients) addressed stimulation of the inferior thalamic peduncle. Twelve studies provided patient-level data and 4 provided pooled data on percentage of responders (ie, >35% reduction in posttreatment Y-BOCS scores). Pooled analysis yielded a global percentage of responders of 60% (95% CI, 49% to 69%). The most frequent adverse events reported were worsening anxiety (25 patients) and hypomanic symptoms (23 patients). Reviewers reported on the benefits and risks of DBS stimulation but could not draw conclusions about stimulation to any particular region or about the safety or efficacy of DBS for OCD compared with sham stimulation or other therapy.

Section Summary: Obsessive-Compulsive Disorder

The literature on DBS for OCD consists of several RCTs and a number of uncontrolled studies. Most studies had small sample sizes. Only 1 of the 5 RCTs identified in a 2015 meta-analysis reported the outcome measure of greatest interest—clinically significant change in Y-BOCS scores. Uncontrolled data have suggested improvements in OCD symptoms after DBS treatment, but have also identified a substantial number of adverse events. Additional blinded controlled studies are needed to draw conclusions about the impact of DBS on the net health benefit.

OTHER INDICATIONS

The evidence on use of DBS for anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, and chronic pain consists of small case series. These case series provide inadequate evidence on which to assess efficacy.

SUMMARY OF EVIDENCE

For individuals who have essential tremor or tremor in PD who receive DBS of the thalamus, the evidence includes a systematic review and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The systematic review (a TEC Assessment) concluded that there was sufficient evidence that DBS of the thalamus results in clinically significant tremor suppression and that outcomes after DBS were at least as good as thalamotomy. Subsequent studies reporting long-term follow-up have supported the conclusions of the TEC Assessment and found that tremors were effectively controlled 5 to 6 years after DBS. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have symptoms (eg, speech, motor fluctuations) associated with PD (advanced or >4 years in duration with early motor symptoms) who receive DBS of the globus pallidus interna (GPi) or subthalamic nucleus (STN), the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One of the systematic reviews (a TEC Assessment) concluded that studies evaluating DBS of the GPi or STN have consistently demonstrated clinically significant improvements in outcomes (eg, neurologic function). Other systematic reviews have also found significantly better outcomes after DBS than after a control intervention. An RCT in patients with levodopa-responsive PD of at least 4 years in duration and uncontrolled motor symptoms found that quality of life at 2 years was significantly higher when DBS was provided in addition to medical therapy. Meta-analyses of RCTs comparing DBS of the GPi with DBS of the STN have reported mixed findings and have not shown that 1 type of stimulation is clearly superior to the other. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary dystonia who receive DBS of the GPi or STN, the evidence includes systematic reviews, an RCT, and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A pooled analysis of 24

studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months). A double-blind RCT found that severity scores improved more after active than after sham stimulation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have tardive dyskinesia or tardive dystonia who receive DBS, the evidence includes case series, one of which included a double-blind comparison of outcomes when the DBS device was turned on versus off. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Few studies were identified and they had small sample sizes (range, 9-19 patients). Additional studies, especially RCTs or other controlled studies, are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have epilepsy who receive DBS, the evidence includes 2 systematic reviews of RCTs and many observational studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Two RCTs were identified. The larger reported that DBS had a positive impact during some parts of the blinded trial phase but not others, and a substantial number of adverse events (in >30% of patients). The smaller RCT (N=16) showed a benefit with DBS. Many small observational studies reported fewer seizures compared with baseline, however, without control groups, interpretation of these results is limited. Additional trials are required to determine the impact of DBS on patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have multiple sclerosis who receive DBS, the evidence includes an RCT. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One RCT with 10 multiple sclerosis patients is insufficient evidence on which to draw conclusions about the efficacy of DBS in this population. Additional trials are required. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Tourette syndrome who receive DBS, the evidence includes crossover RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Several small (≤15 patients) crossover trials and a 2015 meta-analysis have suggested that DBS may improve outcomes in patients with Tourette syndrome. However, the optimal target of the brain for DBS is unknown, so additional controlled studies in larger numbers of patients are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cluster headaches or facial pain who receive DBS, the evidence includes a randomized crossover study and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. In the randomized study, the between-group difference in response rates did not differ significantly between active and sham stimulation phases. Additional RCTs or controlled studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have treatment-resistant depression who receive DBS, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The only double-blind, parallel-group RCT in patients with depression did not find that DBS significantly increased the response rate compared with sham; 2 other RCTs were stopped due to futility. A crossover controlled trial randomized patients to active or to sham stimulation after a year of open-label stimulation. There was a greater reduction in symptom scores after active stimulation, but only in patients who were responders in the open-

label phase; these findings might not be generalizable. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have obsessive-compulsive disorder who receive DBS, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Among the RCTs on DBS for obsessive-compulsive disorder, only one has reported the outcome of greatest clinical interest (therapeutic response rate), and that trial did not find a statistically significant benefit for DBS compared with sham treatment. The evidence is insufficient to determine the effects of the technology on health

For individuals who have anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, or chronic pain who receive DBS, the evidence includes case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. RCTs are needed to evaluate the efficacy of DBS for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 academic medical centers and 2 physician specialty societies while this policy was under review in 2014. Input supported the use of bilateral deep brain stimulation in patients with medically unresponsive tremor in both limbs.

PRACTICE GUIDELINES AND POSITION STATEMENTS
European Academy of Neurology
In 2016, the European Academy of Neurology published guidelines on neuromodulation in management of chronic pain.[52] Due to "very low" quality of evidence, the Academy could not recommend deep brain stimulation (DBS) for treatment of neuropathic pain.

American Academy of Neurology

Essential Tremor
The American Academy of Neurology (AAN) updated its guidelines on the treatment of essential tremor (ET) in 2011.[53] This update did not change the conclusions and recommendations of AAN 2005 practice parameters on DBS for ET.[54] The guidelines stated that bilateral DBS of the thalamic nucleus may be used to treat medically refractory limb tremor in both upper limbs (level C, possibly effective), but that there were insufficient data on the risk/benefit ratio of bilateral vs unilateral DBS in the treatment of limb tremor. There was insufficient evidence to make recommendations on the use of thalamic DBS for head or voice tremor (level U, treatment is unproven).

Parkinson Disease
The 2006 guidelines from AAN on the treatment of Parkinson disease (PD) with motor fluctuations and dyskinesia found that, although criteria are evolving, patients with PD considered candidates for DBS include those who are levodopa-responsive, nondemented, and neuropsychiatrically intact patients who have intractable motor fluctuations, dyskinesia, or tremor.[55] AAN concluded that DBS of the subthalamic nucleus (STN) may be considered a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (level C,

possibly effective), but found evidence insufficient to make any recommendations about the effectiveness of DBS of the globus pallidus or the ventral intermediate nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients.

The 2010 guidelines from AAN on the treatment of nonmotor symptoms of PD found insufficient evidence for the treatment of urinary incontinence with DBS of the STN.[56] AAN found that DBS of the STN possibly improves sleep quality in patients with advanced PD. However, none of the studies performed DBS to treat insomnia as a primary symptom, and DBS of the STN is not currently used to treat sleep disorders.

Tardive Syndromes
The 2013 guidelines[57] from AAN on the treatment of tardive syndromes were updated in 2018.[58] The latest guidelines state that "pallidal DBS possibly improves tardive dyskinesia and might be considered as a treatment for intractable tardive dyskinesia (Level C, which indicates that the treatment is possibly effective, based on ≥1 class II study and consistent with ≥2 class III studies).

European Society for the Study of Tourette Syndrome
The European Society for the Study of Tourette Syndrome published guidelines on DBS in 2011.[59] The guidelines stated that DBS for Tourette syndrome is still in its infancy and that there were no randomized controlled trials that have included a sufficiently large number of patients. The Society suggested that DBS only be used in adult, treatment-resistant, and severely affected patients, and highly recommended that DBS be performed in the context of controlled and double-blind trials including larger and carefully characterized groups of patients.

Canadian Network for Mood and Anxiety Treatments
The Canadian Network for Mood and Anxiety Treatments' 2009 clinical guidelines for management of major depressive disorder in adults found emerging evidence to support DBS as an experimental intervention for patients with treatment-refractory depression.[60] There was no consensus on the most effective target brain region for implantation, although 3 regions have been explored (subcallosal cingulated gyrus, nucleus accumbens, ventral caudate/ventral striatum region).

American Society for Stereotactic and Functional Neurosurgery et al
The American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons published a joint systematic review and guidelines on DBS for obsessive-compulsive disorder (OCD) in 2014.[48] The document concluded that there was a single level I study supporting the use of bilateral STN DBS for medically refractory OCD and a single level II study supporting bilateral nucleus accumbens DBS for medically refractory OCD. It also concluded that the evidence on unilateral DBS was insufficient.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) has published guidance documents on DBS, as discussed in the following subsections.

Tremor and Dystonia
In 2006, NICE made the same statements about use of DBS for treatment of both tremor and dystonia.[61] Unilateral and bilateral stimulation of structures responsible for modifying movements, such as the thalamus, globus pallidus, and the STN, which interact functionally with the substantia nigra, are included in both guidance statements. The guidance stated: "Current evidence on the

safety and efficacy of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) appears adequate to support the use of this procedure."

Refractory Chronic Pain Syndromes (Excluding Headache)

The 2011 guidance from NICE indicated there is evidence that DBS for refractory chronic pain (excluding headache) is associated with serious risks.[62] However, the procedure is "efficacious in some patients" refractory to other treatments." Patients should be informed that DBS may not control their chronic pain symptoms and that possible risks associated with this procedure include the small risk of death.

Intractable Trigeminal Autonomic Cephalalgias

The 2011 guidance from NICE indicated that the evidence on the efficacy of DBS for intractable trigeminal autonomic cephalalgias (eg, cluster headaches) was "limited and inconsistent, and the evidence on safety shows that there were serious but well-known adverse effects."[63]

Refractory Epilepsy

The 2012 guidance from NICE indicated that the evidence on the efficacy of DBS for refractory epilepsy was limited in both quantity and quality: "The evidence on safety showed that there are serious but well-known adverse effects.[64]

Parkinson Disease

In 2003, NICE stated that the evidence on the safety and efficacy of DBS for treatment of Parkinson disease "appears adequate to support the use of the procedure."[65] The guidance noted that DBS should only be offered when Parkinson disease is refractory to best medical treatment.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01801319	A Clinical Evaluation of Subcallosal Cingulate Gyrus Deep Brain Stimulation for Treatment-Resistant Depression	40	Dec 2017 (ongoing)
NCT00640133	Effectiveness of Deep Brain Stimulation for Treating People with Treatment Resistant Obsessive-Compulsive Disorder	27	Feb 2018
NCT01983904	DBS for Treatment Resistant Depression (CRIO-DBS)	25	Mar 2018
NCT00367003	Deep Brain Stimulation for Treatment Resistant Depression	20	Sep 2018
NCT02782533	DBS of the Third Ventricle for Cluster Headache and Obesity (DBS V3)	15	Nov 2018
NCT02601677	Deep Brain Stimulation of NAc/ALIC to Prevent Treatment-Refractory Obsessive Compulsive Disorder	10	Nov 2018
NCT02480803	Treatment in Advanced Parkinson's Disease: Continuous Intrajejunal Levodopa INfusion VErsus Deep Brain Stimulation	66	Dec 2018
NCT01329133	Deep Brain Stimulation and Obsessive-Compulsive Disorder (STOC2)	31	Jan 2019

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02773082[a]	Reclaim™ Deep Brain Stimulation (DBS) Therapy for Obsessive-Compulsive Disorder (OCD) (DBS)	50	Jan 2019
NCT02076698	Clinical and Medico-economical Assessment of Deep Brain Stimulation of the Anterior Nucleus of the Thalamus for the Treatment of Pharmacoresistant Partial Epilepsy	62	Dec 2019
NCT02056873	Tourette Syndrome Deep Brain Stimulation	20	Dec 2019
NCT01973478	Deep Brain Stimulation in Patients With Chronic Treatment Resistant Depression	40	Feb 2020
NCT01817517	Thalamic Deep Brain Stimulation for the Treatment of Refractory Tourette Syndrome	10	Apr 2020
NCT02535884[a]	Deep Brain Stimulation (DBS) of the Globus Pallidus (GP) in Huntington's Disease (HD) (HD-DBS)	50	Oct 2020
NCT01210781	Target Planning for Placement of DBS-electrodes and Follow-Up of the Clinical Efficacy of Stimulation	100	Dec 2020
NCT02937688[a]	Deep Brain Stimulation (DBS) for Parkinson's Disease International Study (REACH-PD)	264	Apr 2021
NCT01839396[a]	Implantable Neurostimulator for the Treatment of Parkinson's Disease (INTREPID)	310	Jul 2021
NCT00855621	Effects of Deep Brain Stimulation in Parkinson's Disease	70	Dec 2023
Unpublished			
NCT02583074	Subthalamic Deep Brain Stimulation in Patients With Medication-Refractory Primary Cranial-Cervical Dystonia: A Randomised, Sham-controlled Trial	40	Sep 2017 (unknown)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy 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. 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.

CPT

Implantation of Electrodes
61850   Twist drill or burr hole for implantation of neurostimulator electrodes, cortical
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 (List separately in addition to primary procedure)
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 (List separately in addition to primary procedure)

Implantation of Pulse Generator

61885   Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array

61886   Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays

Electronic Analysis

95970   Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact groups[s], interleaving, amplitutde, pulse width, frequency [Hz], on/off cycling, burst magnet mode, dose lockout, patient selectable parametrs, responsive neurostimulation, detection alogrithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve neurostimulator pulse generator/transmitter, without reprogramming

95976   Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

95977   Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

95983   Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, doe lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional

95984   Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, doe lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional

HCPCS
L8680   Implantable neurostimulator electrode, each
L8685   Implantable neurostimulator pulse generator, single array, rechargeable, includes
           extension
L8686   Implantable neurostimulator pulse generator, single array, nonrechargeable, includes
           extension
L8687   Implantable neurostimulator pulse generator, dual array, rechargeable, includes
           extension
L8688   Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes
           extension

▪ Coding for deep brain stimulation consists of a series of CPT codes describing the various steps
  of the procedure; ie, implantation of the electrodes, implantation of the pulse generator,
  intraoperative monitoring and programming of the electrodes, and postoperative
  neuroprogramming.
▪ 61863, 61864, 61867, 61868 recognize the option of the implantation of electrodes using
  microelectrode recording or not. In addition, if the patient is undergoing bilateral implantation of
  electrodes, one of the "each additional array" codes may be used. In some instances, patients
  undergo bilateral implantation in a staged procedure.
▪ Neurostimulator analysis and programming is classified as either simple or complex. CPT codes
  95978 and 95979 are time based. Simple neurostimulators are defined as those affecting 3 or
  fewer neurostimulatory parameters (eg, pulse amplitude, duration, frequency, number of
  electrode contacts) while a complex device affects more than 3 parameters. In the setting of
  deep brain stimulation for tremor control, it is anticipated that the neuroprogramming and
  analysis would be classified as simple. However, deep brain stimulation of the globus pallidus
  and subthalamic nucleus stimulation requires intraoperative monitoring of more than 1 clinical
  feature, (ie, rigidity, dyskinesia, tremor) and the neuroprogramming would probably be classified
  as complex.
▪ Over time, patients may undergo several sessions of electronic analysis and programming to find
  the optimal programming parameters. CPT codes 95970, 95978, and 95979, may be used.

ICD-10 Diagnoses (Effective October 1, 2015)
G20   Parkinson's disease
G21.11   Neuroleptic induced parkinsonism
G21.19   Other drug induced secondary parkinsonism
G21.2   Secondary parkinsonism due to other external agents
G21.3   Postencephalitic parkinsonism
G21.4   Vascular parkinsonism
G24.1   Genetic torsion dystonia
G24.2   Idiopathic nonfamilial dystonia
G24.3   Spasmodic torticollis
G24.9   Dystonia, unspecified
G25.0   Essential tremor
G25.1   Drug-induced tremor
G25.2   Other specified forms of tremor

REVISIONS	
06-13-2011	Updated Description section.
	In the Policy Title section, removed "of the Thalamus" to read "Deep Brain Stimulation."
	In the Policy Language section: • Item III, A, added ", and tardive dyskinesia" to read "Other movement disorders, including but not limited to multiple sclerosis, post-traumatic dyskinesia, and tardive dyskinesia." • Item III, C, added "Other psychiatric or neurologic disorder, including but not limited to Tourette syndrome," and ", depression, and epilepsy" to read "other psychiatric or neurologic disorder, including but not limited to Tourette syndrome, obsessive compulsive disorder, depression, and epilepsy."
	Added Policy Guidelines
	Updated Rationale section.
	In the Coding section: • Removed CPT codes: 61567, 95971. • Removed HCPCS codes: L8681, L8682, and L8683. • Added CPT codes: 95970. • Deleted Diagnosis code, 333.7. Code requires a 5th digit. • Added Diagnosis codes: 333.79, 333.89.
	Revision section added.
	In the Reference section: • Updated Reference section. • Added "Other References" section.
09-17-2013	Updated Description section.
	In Policy section: ▪ In Item III, C, added "anorexia nervosa, alcohol addiction, chronic pain," to read "other psychiatric or neurologic disorder, including but not limited to Tourette syndrome, obsessive compulsive disorder, depression, anorexia nervosa, alcohol addiction, chronic pain, and epilepsy."
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis codes *(Effective October 1, 2014)*
	Updated Reference section.
02-10-2015	Description section updated
	In Policy section: ▪ Added the medically necessary indication of "Bilateral deep brain stimulation of the thalamus may be considered medically necessary in patients with disabling, medically unresponsive tremor in both limbs due to essential tremor or Parkinson disease." ▪ In Item III A 2 added "motor portion of the" to read, "a minimal score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale…" ▪ In Item III B revised "greater" to "older" to read, "Patients aged older than 7 years with…" ▪ In Item IV C added "Alzheimer disease" to the experimental / investigational indications to read, "other psychiatric or neurologic disorder, including but not limited to Tourette syndrome, depression, obsessive-compulsive disorder, Alzheimer disease, anorexia nervosa, alcohol addiction, chronic pain, and epilepsy"
	Rationale section updated
	In Coding section: ▪ Updated nomenclature in CPT/HCPCS codes: 61864, 61868, 61886, 95970, 95979 ▪ Added Coding instructions
	References updated
05-24-2017	Description section updated

REVISIONS

	In Policy section: ▪ In Item II added "upper" to read "Bilateral deep brain stimulation of the thalamus may be considered medically necessary in patients with disabling, medically unresponsive tremor in both upper limbs due to essential tremor or Parkinson disease." ▪ In Item III A 3 added "ONE of the following:" and "OR Parkinson disease for at least 4 years" to read "ONE of the following: a) a minimal score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours OR b) Parkinson disease for at least 4 years"
	Rationale section updated
	In Coding section: ▪ Updated a coding notation
	References updated
01-01-2019	Definition section updated
	Rationale section updated
	In Coding section: ▪ Added CPT Codes: 95976, 95977, 95983, 95984 ▪ Removed CPT Codes: 95978, 95979 ▪ Revised CPT Code: 95970
	References updated

REFERENCES

1.   Blue Cross and Blue Shield Technology Evaluation Center. Deep brain stimulation of the thalamus for tremor. *TEC Assessment.* 1997;Volume 12:Tab 20.
2.   Schuurman PR, Bosch DA, Merkus MP, et al. Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. *Mov Disord.* Jun 15 2008;23(8):1146-1153. PMID 18442104
3.   Hariz MI, Krack P, Alesch F, et al. Multicentre European study of thalamic stimulation for parkinsonian tremor: a 6 year follow-up. *J Neurol Neurosurg Psychiatry.* Jun 2008;79(6):694-699. PMID 17898034
4.   Putzke JD, Uitti RJ, Obwegeser AA, et al. Bilateral thalamic deep brain stimulation: midline tremor control. *J Neurol Neurosurg Psychiatry.* May 2005;76(5):684-690. PMID 15834027
5.   Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. *J Neurosurg.* Apr 2006;104(4):506-512. PMID 16619653
6.   Pollo C, Kaelin-Lang A, Oertel MF, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain.* Jul 2014;137(Pt 7):2015-2026. PMID 24844728
7.   Steigerwald F, Muller L, Johannes S, et al. Directional deep brain stimulation of the subthalamic nucleus: A pilot study using a novel neurostimulation device. *Mov Disord.* Aug 2016;31(8):1240-1243. PMID 27241197
8.   Rebelo P, Green AL, Aziz TZ, et al. Thalamic Directional Deep Brain Stimulation for tremor: Spend less, get more. *Brain Stimul.* Jan 6 2018. PMID 29373260
9.   Dembek TA, Reker P, Visser-Vandewalle V, et al. Directional DBS increases side-effect thresholds-A prospective, double-blind trial. *Mov Disord.* Oct 2017;32(10):1380-1388. PMID 28843009
10.   Blue Cross and Blue Shield Technology Evaluation Center. Bilateral deep brain stimulation of the subthalamic nucleus or the globus pallidus interna for treatment of advanced Parkinson's disease. *TEC Assessment.* 2001;Volume 16:Tab 16.
11.   Perestelo-Perez L, Rivero-Santana A, Perez-Ramos J, et al. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. *J Neurol.* Nov 2014;261(11):2051-2060. PMID 24487826
12.   Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord.* Jun 2006;21(Suppl 14):S290-304. PMID 16892449

13.	Appleby BS, Duggan PS, Regenberg A, et al. Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: A meta-analysis of ten years' experience. *Mov Disord.* Sep 15 2007;22(12):1722-1728. PMID 17721929

14.	Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med.* Feb 14 2013;368(7):610-622. PMID 23406026

15.	Sako W, Miyazaki Y, Izumi Y, et al. Which target is best for patients with Parkinson's disease? A meta-analysis of pallidal and subthalamic stimulation. *J Neurol Neurosurg Psychiatry.* Sep 2014;85(9):982-986. PMID 24444854

16.	Combs HL, Folley BS, Berry DT, et al. Cognition and depression following deep brain stimulation of the subthalamic nucleus and globus pallidus pars internus in Parkinson's disease: a meta-analysis. *Neuropsychol Rev.* Dec 2015;25(4):439-454. PMID 26459361

17.	Tan ZG, Zhou Q, Huang T, et al. Efficacies of globus pallidus stimulation and subthalamic nucleus stimulation for advanced Parkinson's disease: a meta-analysis of randomized controlled trials. *Clin Interv Aging.* Jul 2016;11:777-786. PMID 27382262

18.	Wang JW, Zhang YQ, Zhang XH, et al. Cognitive and psychiatric effects of STN versus GPi deep brain stimulation in Parkinson's disease: a meta-analysis of randomized controlled trials. *PLoS One.* Jun 2016;11(6):e0156721. PMID 27248139

19.	Xie CL, Shao B, Chen J, et al. Effects of neurostimulation for advanced Parkinson's disease patients on motor symptoms: A multiple-treatments meta-analysas of randomized controlled trials. *Sci Rep.* May 04 2016;6:25285. PMID 27142183

20.	Xu F, Ma W, Huang Y, et al. Deep brain stimulation of pallidal versus subthalamic for patients with Parkinson's disease: a meta-analysis of controlled clinical trials. *Neuropsychiatr Dis Treat.* Jul 2016;12:1435-1444. PMID 27382286

21.	U.S. Food and Drug Administration. Summary of Safety and Probable Benefit. Medtronic Activa Dystonia Therapy. 2003; http://www.accessdata.fda.gov/cdrh_docs/pdf2/H020007b.pdf. Accessed February 22, 2018.

22.	Moro E, LeReun C, Krauss JK, et al. Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. *Eur J Neurol.* Apr 2017;24(4):552-560. PMID 28186378

23.	Volkmann J, Mueller J, Deuschl G, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. *Lancet Neurol.* Sep 2014;13(9):875-884. PMID 25127231

24.	Damier P, Thobois S, Witjas T, et al. Bilateral deep brain stimulation of the globus pallidus to treat tardive dyskinesia. *Arch Gen Psychiatry.* Feb 2007;64(2):170-176. PMID 17283284

25.	Gruber D, Trottenberg T, Kivi A, et al. Long-term effects of pallidal deep brain stimulation in tardive dystonia. *Neurology.* Jul 7 2009;73(1):53-58. PMID 19564584

26.	Pouclet-Courtemanche H, Rouaud T, Thobois S, et al. Long-term efficacy and tolerability of bilateral pallidal stimulation to treat tardive dyskinesia. *Neurology.* Feb 16 2016;86(7):651-659. PMID 26791148

27.	Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. *Epilepsia.* Feb 2018;59(2):273-290. PMID 29218702

28.	Bouwens van der Vlis TAM, Schijns O, Schaper F, et al. Deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy. *Neurosurg Rev.* Jan 6 2018. PMID 29306976

29.	Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia.* May 2010;51(5):899-908. PMID 20331461

30.	Troster AI, Meador KJ, Irwin CP, et al. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. *Seizure.* Feb 2017;45:133-141. PMID 28061418

31.	Cukiert A, Cukiert CM, Burattini JA, et al. Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study. *Epilepsia.* Oct 2017;58(10):1728-1733. PMID 28744855

32.	Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology.* Mar 10 2015;84(10):1017-1025. PMID 25663221

33.	Kim SH, Lim SC, Kim J, et al. Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience. *Seizure.* Nov 2017;52:154-161. PMID 29040867

34. Baldermann JC, Schuller T, Huys D, et al. Deep brain stimulation for Tourette-syndrome: a systematic review and meta-analysis. *Brain Stimul.* Mar-Apr 2016;9(2):296-304. PMID 26827109
35. Fraint A, Pal G. Deep brain stimulation in Tourette's syndrome. *Front Neurol.* Aug 2015;6:170. PMID 26300844
36. Schrock LE, Mink JW, Woods DW, et al. Tourette syndrome deep brain stimulation: a review and updated recommendations. *Mov Disord.* Apr 2015;30(4):448-471. PMID 25476818
37. Servello D, Zekaj E, Saleh C, et al. Sixteen years of deep brain stimulation in Tourette's Syndrome: a critical review. *J Neurosurg Sci.* Jun 2016;60(2):218-229. PMID 26788742
38. Piedad JC, Rickards HE, Cavanna AE. What patients with Gilles de la Tourette syndrome should be treated with deep brain stimulation and what is the best target? *Neurosurgery.* Jul 2012;71(1):173-192. PMID 22407075
39. Kefalopoulou Z, Zrinzo L, Jahanshahi M, et al. Bilateral globus pallidus stimulation for severe Tourette's syndrome: a double-blind, randomised crossover trial. *Lancet Neurol.* Jun 2015;14(6):595-605. PMID 25882029
40. Fontaine D, Lazorthes Y, Mertens P, et al. Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. *J Headache Pain.* Feb 2010;11(1):23-31. PMID 19936616
41. Bussone G, Franzini A, Proietti Cecchini A, et al. Deep brain stimulation in craniofacial pain: seven years' experience. *Neurol Sci.* May 2007;28(Suppl 2):S146-149. PMID 17508162
42. Broggi G, Franzini A, Leone M, et al. Update on neurosurgical treatment of chronic trigeminal autonomic cephalalgias and atypical facial pain with deep brain stimulation of posterior hypothalamus: results and comments. *Neurol Sci.* May 2007;28(Suppl 2):S138-145. PMID 17508161
43. Morishita T, Fayad SM, Higuchi MA, et al. Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. *Neurotherapeutics.* Jul 2014;11(3):475-484. PMID 24867326
44. Mosley PE, Marsh R, Carter A. Deep brain stimulation for depression: Scientific issues and future directions. *Aust N Z J Psychiatry.* Nov 2015;49(11):967-978. PMID 26276049
45. 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.* Aug 15 2015;78(4):240-248. PMID 25726497
46. 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.* May 01 2016;73(5):456-464. PMID 27049915
47. de Koning PP, Figee M, van den Munckhof P, et al. Current status of deep brain stimulation for obsessive-compulsive disorder: a clinical review of different targets. *Curr Psychiatry Rep.* Aug 2011;13(4):274-282. PMID 21505875
48. 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.* Oct 2014;75(4):327-333; quiz 333. PMID 25050579
49. Alonso P, Cuadras D, Gabriels L, et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. *PLoS One.* Jul 2015;10(7):e0133591. PMID 26208305
50. Kisely S, Hall K, Siskind D, et al. Deep brain stimulation for obsessive-compulsive disorder: a systematic review and meta-analysis. *Psychol Med.* Dec 2014;44(16):3533-3542. PMID 25066053
51. Naesstrom 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.* Oct 2016;70(7):483-491. PMID 27103550
52. Cruccu G, Garcia-Larrea L, Hansson P, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur J Neurol.* Oct 2016;23(10):1489-1499. PMID 27511815
53. Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology.* Nov 8 2011;77(19):1752-1755. PMID 22013182

54.   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.* Jun 28 2005;64(12):2008-2020. PMID 15972843

55.   Pahwa R, Factor SA, Lyons KE, et al. Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* Apr 11 2006;66(7):983-995. PMID 16606909

56.   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.* Mar 16 2010;74(11):924-931. PMID 20231670

57.   Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* Jul 30 2013;81(5):463-469. PMID 23897874

58.   Bhidayasiri R, Jitkritsadakul O, Friedman JH, et al. Updating the recommendations for treatment of tardive syndromes: A systematic review of new evidence and practical treatment algorithm. *J Neurol Sci.* Feb 5 2018. PMID 29454493

59.   Muller-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.* Apr 2011;20(4):209-217. PMID 21445726

60.   Kennedy SH, Milev R, Giacobbe P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. *J Affect Disord.* Oct 2009;117(Suppl 1):S44-53. PMID 19656575

61.   National Institute for Health and Care Excellence (NICE). Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) [IPG188]. 2006; https://www.nice.org.uk/guidance/ipg188. Accessed February 22, 2018.

62.   National Institute for Health and Care Excellence (NICE). Deep brain stimulation for refractory chronic pain syndromes (excluding headache) [IPG382]. 2011; http://guidance.nice.org.uk/IPG382. Accessed February 22, 2018.

63.   National Institute for Health and Care Excellence (NICE). Deep brain stimulation for intractable trigeminal autonomic cephalalgias [IPG381]. 2011; http://www.nice.org.uk/IPG381. Accessed February 22, 2018.

64.   National Institute for Health and Care Excellence (NICE). Deep brain stimulation for refractory epilepsy [IPG416]. 2012; http://guidance.nice.org.uk/IPG416. Accessed February 22, 2018.

65.   National Institute for Health and Care Excellence (NICE). Deep brain stimulation for Parkinson's disease [IPG19]. 2003; https://www.nice.org.uk/guidance/ipg19. Accessed February 22, 2018.

66.   Centers for Medicare & Medicaid (CMS). National Coverage Determination (NCD) for Deep Brain Stimulation for Essential Tremor and Parkinson's Disease (160.24). 2003; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=279&ncdver=1&DocID=160.24&bc=gAAAABAAAAAA&. Accessed February 22, 2018.

Other References

1.   Blue Cross and Blue Shield of Kansas Behavioral Health Liaison Committee, June 6, 2006 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC–02-06).

2.   Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, August 6, 2006 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC–02-06).