
Medical Policy



Nonprofit corporations and independent licensees
of the Blue Cross and Blue Shield Association

Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 3/1/21**
(See policy history boxes for previous effective dates)

Title: Deep Brain Stimulation

Description/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.

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 the following components: the implantable neurostimulator, the 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 stimulation, and a patient

control magnet, which allows the patient to turn the neurostimulator on and off, or change between high and low settings.

The FDA-labeled indications for Activa® were originally limited to unilateral implantation for the treatment of tremor, but, the indications have evolved over time. In 2002, the FDA labeled indications were expanded to include bilateral implantation as a treatment to decrease the symptoms of advanced PD 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." In 2018, the deep brain stimulation system received an expanded indication as an adjunctive therapy for epilepsy (P960009 S318). Other deep brain stimulation systems are described in Table 1.

Table 1. Deep Brain Stimulation Systems

System	Manufacturer	Features	PMA or HDE	Approval Date	Indications
Activa® Deep Brain Stimulation Therapy System	Medtronic		P96009	1997	Unilateral or bilateral stimulation of the internal globus pallidus or subthalamic nucleus for symptoms of Parkinson disease or primary dystonia
Reclaim® DBS Therapy for Obsessive Compulsive Disorder	Medtronic	Approved for OCD	H050003	2009	Bilateral stimulation of the anterior limb of the internal capsule for severe obsessive-compulsive disorder
Brio Neurostimulation System	St. Jude Medical		P140009	2015	Parkinsonian tremor (subthalamic nucleus) and essential tremor (thalamus)
Infinity DBS	St. Jude Medical	Directional leads that "steer" current, reducing side effects.	P140009	2016	Parkinsonian tremor
Vercise DBS System	Boston Scientific	Directional leads	P150031	2017	Moderate-to-advanced levodopa-responsive PD inadequately controlled with medication alone

DBS: deep brain stimulation; HDE: humanitarian device exemption; OCD: obsessive-compulsive disorder; PD: Parkinson disease; PMA: premarket approval

FDA product code: OLM, PJS, NHL, MHY.

Medical Policy Statement

The safety and effectiveness of unilateral deep brain stimulation of the thalamus is established. It may be considered a useful therapeutic option in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson’s disease.

The safety and effectiveness of bilateral deep brain stimulation of the thalamus have been established. It may be considered a useful therapeutic option in patients with disabling,

medically unresponsive tremor in both upper limbs due to essential tremor or Parkinson disease.

The safety and effectiveness of unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus have been established. It may be considered a useful adjunctive therapeutic option in patients with medically refractory Parkinson's disease, essential tremor or primary dystonia.

Deep brain stimulation for other movement disorders, including but not limited to tardive dyskinesia, multiple sclerosis and post-traumatic dyskinesia, is considered experimental/investigational. The safety and effectiveness of this treatment for these conditions have not been established.

Deep brain stimulation for the treatment of other psychiatric or neurologic disorders, including but not limited to Tourette syndrome, depression, obsessive-compulsive disorder, Alzheimer disease, anorexia nervosa, alcohol addiction, chronic pain, epilepsy and chronic cluster headaches, is considered experimental/investigational. The safety and effectiveness of this treatment for these conditions have not been established.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Unilateral deep brain stimulation of the thalamus may be indicated in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson disease.

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

Unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus may be indicated as an adjunct therapy in the following patients:

- Those with Parkinson disease with ALL of the following:
 - A good response to levodopa; **AND**
 - Motor complications not controlled by pharmacologic therapy; **AND**
 - One of the following:
 - 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**
 - Parkinson disease for at least 4 years
- Patients aged greater than 7 years with chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis)
- Essential tremors

Disabling, medically unresponsive tremor is defined as all of the following:

- tremor causing significant limitation in daily activities
- inadequate control by maximal dosage of medication for at least 3 months before implant

Exclusions:

- Deep brain stimulation for other movement disorders, including but not limited to multiple sclerosis, post-traumatic dyskinesia, and tardive dyskinesia
 - Deep brain stimulation for the treatment of chronic cluster headaches
 - Deep brain stimulation for the treatment of other psychiatric or neurologic disorders, including but not limited to Tourette syndrome, depression, obsessive-compulsive disorder, Alzheimer disease, anorexia nervosa, alcohol addiction, chronic pain, and epilepsy
 - Movement disorders from other causes not noted above
 - Patients who have cognitive impairments
 - Such as patients who have dementia that may interfere with the ability to cooperate
 - Inability to comply and participate with the treatment plan
 - Patients who are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker
 - Patients who have medical conditions that require repeated magnetic resonance imaging (MRI)
 - Patients who have had botulinum toxin injections within the last 6 months
-

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

61850	61863	61864	61867	61868	61880
61885	61886	61888	95970	95983	95984

Other codes (investigational, not medically necessary, etc.):

64999

Note: The above code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), 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 technology, two domains are examined: the relevance, 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

Clinical Context and Therapy Purpose

Deep brain stimulation (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 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.

The question addressed in this evidence review is: Does DBS improve the net health outcome in patients with essential tremor or Parkinson Disease

The following PICO's were used to select literature to inform this review.

Patients

The relevant population(s) of interest are patients with essential tremor or symptoms associated with Parkinson disease (PD).

Interventions

The therapy being considered is deep brain stimulation, unilateral or bilateral stimulation of the thalamus as well stimulation of the internal segment of the globus pallidus interna and subthalamic nucleus.

Comparators

PD is usually treated with medication. Surgery may be considered in people who respond poorly to medication, have severe side-effects, or have severe fluctuations in response to medication.

Outcomes

Key efficacy outcomes include motor scores, mobility, disability, activities of daily living and quality of life.

Key safety outcomes include death, stroke, depression, cognition infection and other device and procedure related events.

Review of Evidence

Unilateral Stimulation of the Thalamus

This section was originally informed by a TEC Assessment (1997) that focused on unilateral 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 side effects 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 five-year follow-up of 68 patients comparing thalamic stimulation with thalamotomy for treatment of tremor due to Parkinson disease (45 patients), essential tremor (13 patients), and multiple sclerosis (10 patients).(2) Forty-eight (71%) patients were assessed at five years: 32 with PD, 10 with ET, and six 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 six months, 3.3 (95% CI, -0.03 to 6.6) at two years, and 4.0 (95% CI, 0.3 to 7.7) at five 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 six years post-surgery, 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, one patient was lost to follow-up due to transfer of care, and one 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 three ($p < 0.05$). Small sample size

limited analysis at months 24 and 36. Dysarthria was reported in six (27%) patients and disequilibrium in five (22%) patients after bilateral stimulation in staged implantations. No patient reported dysarthria and two 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 eight had bilateral implantation.(5) Sixteen patients with unilateral and 7 with bilateral stimulators completed at least part of the five-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 five-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. 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.

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 supported the conclusions of the 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.

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 is 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 to 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 two trials and the randomization method was described in four 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 was 0.3% to 0.7%.(13) The completed suicide rate was 0.16% to 0.32%. In light of the rate of suicide in patients treated with DBS, reviewers argued for prescreening patients for suicide risk.

PD With Early Motor Complications

Schuepbach et al (2013) published an RCT evaluating DBS in patients with PD and early motor cortex complications.(14) Key eligibility criteria included age 18 to 60 years, disease duration of at least four years, improvement of motor signs of at least 50% with dopaminergic medication, and PD disease severity below stage III 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 two years.

The primary end point was mean change from baseline to two 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 three 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 one serious adverse event. This included 26 serious adverse events in the DBS group that were surgery- or device-related; reoperation was necessary in four patients.

Globus Pallidus Interna versus Subthalamic Nucleus Stimulation

A number of meta-analyses have compared the efficacy of GPi and STN stimulation in PD patients.(15-21) 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 (BDI) II, levodopa-adjusted dose (LED), neurocognitive status, or QOL. Ten RCTs met eligibility criteria and were included in the quantitative synthesis. After six months, there were no significant differences in the UPDRS-III scores between the GPi and STN groups for patients in the off-medication/on-stimulation 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 one to three 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 (six studies; MD=0.60; 95% CI, 0.46 to 0.74). However, the analysis of BDI-II scores favored the GPi group (four studies; MD = -0.31; 95% CI, -0.51 to -0.12). Other meta-analyses had similar mixed findings and none concluded that one 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 four years in duration and uncontrolled motor symptoms. The trial found that QOL at two 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 one type of stimulation was clearly superior to the other.

DYSTONIA

Clinical Context and Therapy Purpose

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.

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.(22) 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 seven years. Among these patients, there was a 60% improvement in clinical scores.

The question addressed in this evidence review is: Does DBS improve the net health outcome in patients with primary or secondary dystonia.

The following PICOs were used to select literature to inform this review.

Patients

The relevant population(s) of interest are patients with primary or secondary dystonia. Primary dystonia is defined when dystonia is the only symptom unassociated with other pathology. 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.

Interventions

The therapy being considered is deep brain stimulation.

Comparators

Treatment options for dystonia include oral or injectable medications (ie, botulinum toxin) and destructive surgical or neurosurgical interventions (ie, thalamotomies or pallidotomies) when conservative therapies fail.

As noted in the FDA humanitarian device exemption HDE analysis of risk and probable benefit, the only other treatment options for chronic refractory primary dystonia are neurodestructive procedures. DBS provides a reversible alternative.

Outcomes

Key efficacy outcomes include clinical severity of dystonia and disability as rated using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) or Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and QOL quality of life.

The Burke-Fahn-Marsden Dystonia Rating Scale total score ranges from 0 to 150. It has two subscales: a movement sub-scale, based on clinical patient examination, that assesses dystonia severity and provoking factors in different body areas, with a maximum score of 120; and a disability sub-scale, that evaluates the patient's report of disability in activities of daily living, for a maximum score of 30. Higher scores correspond to greater levels of morbidity. There is currently no established minimally important difference in the Burke-Fahn-Marsden Dystonia Rating Scale total score.

Toronto Western Spasmodic Torticollis Rating scale (TWSTRS) is most commonly used to assess the status of people with cervical dystonia. The Toronto Western Spasmodic Torticollis Rating scale has a total score ranging from 0 to 85. It is a composite of three sub-scales: severity which ranges from 0 to 35; disability which ranges from 0 to 30; and pain which ranges from 0 to 20. Higher scores correspond to greater levels of morbidity.

Key safety outcomes include death, stroke, depression, cognition, infection and other device and procedure related events.

PRIMARY DYSTONIA

Systematic Reviews

Moro et al (2017) published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia).(23) 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 three controlled studies, two RCTs (Kupsch et al [2006] and Volkmann et al [2014]; described below) and 1 study that included a double-blind evaluation with and without stimulation. Rodrigues et al (2019) performed a Cochrane systematic review of RCTs and identified the same two RCTs.(24)

Randomized Controlled Trials

The two RCTs identified in the systematic reviews are described in Tables 2-5. Kupsch et al (2006) randomized 40 patients with primary segmental or generalized dystonia to DBS or sham stimulation for three months.(75) The primary outcome was change from baseline to three months in the severity of symptoms measured by the BFMDRS assessed by blinded reviewers from videotaped sessions. All patients subsequently received open-label DBS for 6 months after blinded treatment. Results are shown in Table 2. In brief, the change from baseline in the mean BFMDRS movement score was significantly greater in the DBS group.

The Volkmann et al (2014) RCT, was a patient- and observer-blinded evaluation of pallidal neurostimulation in subjects with refractory cervical dystonia.(26) The primary outcome was change in the Toronto Western Spasmodic Torticollis Rating scale severity score at the end of the blinded study period (3 months); thereafter, all patients received open-label active stimulation. Results are shown in Table 3. There was significantly greater improvement in the neurostimulation group than in the sham group on the Toronto Western Spasmodic Torticollis Rating scale disability score and the Bain Tremor Scale score but not on the Toronto Western

Spasmodic Torticollis Rating scale 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.

Table 2. Characteristics of RCTs of DBS from Primary Dystonia

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Kupsch (2006); NCT00142259	Germany, Norway, Austria	10	2002 to 2004	Patients ages 14 to 75 years with marked disability owing to primary generalized or segmental dystonia despite optimal pharmacologic treatment with disease duration of at least 5 years	N=20 GPI DBS	N=20 Sham
Volkman (2014); NCT00148889	Germany, Norway, Austria	10	2006 to 2008	Adults under age of 75 with idiopathic or inherited isolated cervical dystonia with disease duration 3 years or longer and ≥ 15 on the TWSTRS	N=32 GPI DBS	N=30 Sham

DBS: deep brain stimulation; GPI: globus pallidus internus; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; RCT: randomized controlled trial.

Table 3. Results of RCTs of DBS for Primary Dystonia

Study	Dystonia Severity	Disability	Quality of Life	Depression Symptoms	Serious Adverse Events
Kupsch (2006)	Change in BFMDRS movement at 3 months, Mean (SD)	Change in BFMDRS disability at 3 months, Mean (SD)	Change in SF-36 at 3 months, Mean (SD)	Change in BDI at 3 months	
N	40	39	33	30	
DBS	-15.8 (14.1)	3.9 (2.9)	PCS: 10.1 (7.4) MCS: 5.2 (15.0)	-5.1 (8.4)	3 (8%) 3 related to lead dislodgement or 1 related to infection requiring hospitalization
Sham	-1.4 (3.8)	0.8 (1.2)	PCS: 3.8 (8.4) MCS: 0.2 (8.7)	-0.5 (10.2)	
Treatment effect (95% CI)	MD = 14.40 (8.0 to 20.80); p<0.01	MD= 3.10 (1.72 to 4.48)	PCS MD=6.30 (1.06 to 11.54) MCS MD=5.00 (-2.14 to 12.14)	MD=4.60 (-2.06 to 11.26)	
Volkman (2014)	Change in TWSTRS severity at 3 months	Change in TWSTRS disability at 3 months	Change in SF-36 at 3 months	Change in BDI at 3 months	
N	62	61	57	61	
DBS	-5.1 (5.1)	-5.6 (5.6)	PCS: 6.6 (21.9) MCS: 11.3 (18.2)	-3.5 (5.6)	16 (26%); 11 related to surgery or device, 1 related to medication or

Sham	-1.3 (2.4)	-1.8 (3.8)	PCS: 3.6 (19.2) MCS: 8.9 (14.4)	-0.4 (3.7)	stimulation, 4 related to dystonia
Treatment effect (95% CI)	MD=3.80 (1.84 to 5.76); p<0.01	MD=3.80 (1.41 to 6.19)	PCS MD=3.00 (-7.71 to 13.71) MCS MD=2.40 (-6.20 to 11.00)	MD=3.10 (0.73 to 5.47)	

BFMDRS: Burke-Fahn-Marsden-Dystonia-Rating-Scale; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; MD: Mean difference; BDI: Beck Depression Inventory; SF-36: short form 36 item quality of life survey, PCS: Physical Component Score; MCS Mental component score; CI: confidence interval; DBS: deep brain stimulation; RCT: randomized controlled trial; SD: standard deviation.

Table 4. Relevance Limitations: RCTs of DBS for Primary Dystonia

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-up ^e
Kupsch (2006)					1: Only 3 months of double-blind study
Volkman (2014)					1: Only 3 months of double blind study

RCT: randomized controlled trial; DBS: deep brain stimulation.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations: RCTs of DBS for Primary Dystonia

Study	Allocation ^a	Blinding ^b	Selective Reporting ^d	Data Completeness ^e	Power ^a	Statistical ^f
Kupsch (2006)			1: Registered after enrollment was complete			
Volkman (2014)		1,3: Treating physicians not blinded. Primary outcome assessors blinded but secondary outcomes subject to bias				

RCT: randomized controlled trial; DBS: deep brain stimulation.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Primary Dystonia

A review prepared for the FDA and systematic reviews have evaluated evidence on DBS for primary dystonia. There are numerous small case series and two RCTs. Both RCTs 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 six months and at last follow-up (mean, 32 months).

TARDIVE DYSKINESIA AND TARDIVE DYSTONIA

Review of Evidence

Randomized Controlled Trials

One RCT has been conducted of pallidal DBS in patients with tardive dystonia. Characteristics are shown in Table 6 and results are in Table 7. Gruber et al (2018) assessed dystonia/dyskinesia severity using the Burke-Fahn- Marsden-Dystonia-Rating-Scale (BFMDRS) at three months between active vs sham DBS.(27) Twenty-five patients were randomized. In the intention-to-treat analyses, the between group difference of dystonia severity was not significant at three months. Adverse events occurred in 10/25 of patients; three of the adverse events were serious. The study was originally powered to include 48 patients but only 25 were randomized and analyses may be underpowered. Study limitations are described in Tables 8 and 9.

Table 6. Characteristics of RCTs of DBS for Tardive Dyskinesia and Tardive Dystonia

Study; Trial	Countries	Sites	Dates	Participants ²	Interventions ¹	
Gruber 2018; MCT00331669	Germany	15	2006 to 2009	Adults with tardive dystonia disease duration of at least 18 months with marked disability and deterioration of activities of daily living owing to tardive dystonia despite	Active N=12	Comparator N=13
					Pallidal DBS	Sham

RCT: randomized controlled trial; DBS: deep brain stimulation.

Table 7. Results of RCTs of DBS for Tardive Dyskinesia and Tardive Dystonia

Study	Dystonia Severity	Disability	Quality of Life	Depression Symptoms	Serious Adverse Events
Gruber 2018	Change in BFMDRS Movement score at 3 months, Mean (SD)	Change in BFMDRS Disability score at 3 months, Mean (SD)	Change in SF-36 at 3 months, Mean (SD)	HAM-D at 3 months, Mean (SD)	
N	25	25	24	24	
DBS	-5.6 (9.1)	0.5 (5.5)	PCS: 5.4 (10.0) MCS: 0.5 (10.9)	1.4 (5.5)	3 events (episodes of confusion, worsening of dystonia following gastrointestinal infection, skin erosion)
Sham	-5.9 (13.9)	-0.3 (1.2)	PCS: 1.6 (7.8) MCS: -0.6 (4.8)	2.2 (6.6)	
Treatment effect (95%)	p=0.72	p=0.43	PCS: p=0.17	p=0.69	

CI)

MCS: p=0.53

BFMDRS: Burke-Fahn-Marsden-Dystonia-Rating-Scale; HAM-D: Hamilton Depression Score; SF-36: short form 36 item quality of life survey, PCS: Physical Component Score; MCS Mental component score; DBS: deep brain stimulation; RCT: randomized controlled trial; SD: standard deviation.

Table 8. Relevance Limitations: RCTs of DBS for Tardive Dyskinesia and Tardive Dystonia

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-up ^e
Gruber 2018					1. 3 months follow-up in blinded period

DBS: deep brain stimulation; RCT: randomized controlled trial.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations: RCTs of DBS for Tardive Dyskinesia and Tardive Dystonia

Study	Allocation ^a	Blinding ^b	Selective Reporting ^d	Data Completeness ^e	Power ^d	Statistical ^f
Gruber 2018				1. Study powered to include 48 patients but only 25 patients enrolled		

DBS: deep brain stimulation; RCT: randomized controlled trial.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Case series

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 on and off positions).(28) 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 9 patients treated with DBS of the GPi for tardive dystonia were reported by Gruber et al (2009).(29) 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.(30) 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 Extrapyrimal 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 an RCT with three months of blinded follow-up and with follow-up of six months to approximately four years. The RCT did not report statistically significant improvement in the dystonia severity outcomes or the secondary outcomes related to disability and QOL for DBS compared to sham but the study did not recruit the number of patients for which it was originally powered. Case series reported favorable results with DBS treatment.

EPILEPSY

Clinical Context and Therapy Purpose

Approximately one-third of patients with epilepsy do not respond to anti-epileptic drugs and are considered to have drug-resistant epilepsy. Patients with drug-resistant or refractory epilepsy have a higher risk of death as well as a high burden of epilepsy-related disabilities and limitations.

The question addressed in this evidence review is: does DBS improve the net health outcome in patients with epilepsy

The following PICO's were used to select literature to inform this review.

Patients

The relevant population(s) of interest are patients with epilepsy refractory to medical treatment who are not candidates for resective surgery. The International League Against Epilepsy defined drug-resistant as failure of adequate trials of two tolerated, appropriately chosen and administered anti-epileptic drugs, used as monotherapy or in combination, to achieve seizure freedom.(31) Patients who are not candidates for resective surgery include those multifocal seizure onset, significant medical comorbidities or generalized-onset epilepsy.

Interventions

The therapy being considered is deep brain stimulation. Several areas of the brain have been targeted.

Comparators

The treatment for chronic epilepsy consists of anti-epileptic drugs (AEDs). A ketogenic diet may be used as an adjunctive treatment. For patients with epilepsy that is refractory to medical treatment, surgery options such as resection or disconnection may be considered.

Vagus nerve stimulation may also be used in patients with drug-refractory epilepsy who are not candidates for resective surgery.

Sham control may be used in RCTs.

Outcomes

Key efficacy outcomes include measures of seizure frequency or severity, response (reduction in seizure frequency by 50% or more), freedom from seizure, functional ability and disability, medication use, hospitalizations and QOL. The Quality of Life Inventory in Epilepsy (QOLIE-31) is a tool used to assess the impact of antiepileptic treatment on patients' lives; the minimally important change in patients with treatment-resistant seizures was five points.(32)

Key safety outcomes include death, stroke, depression, cognition infection and other device and procedure related events.

Study Selection Criteria

1. To assess efficacy outcomes, comparative controlled prospective trials were included, with preference for randomized controlled trials.
2. In the absence of such trials, comparative observational studies, with preference for prospective studies will be included.
3. To assess longer-term outcomes and adverse effects, single arm studies that captured longer periods of follow-up and/or larger populations may be included.
4. Studies with duplicative or overlapping populations will be excluded.

Review of Evidence

Systematic Review

A Cochrane systematic review on deep brain and cortical stimulation for epilepsy was published in 2017 and included RCTs published through 2016.(33)The review included one trial on anterior thalamic nucleus DBS for multifocal epilepsy (n=109, see discussion in following section), one trial on centromedian thalamic DBS for multifocal or generalized epilepsy (n=7), and three RCTs on hippocampal DBS for medial temporal lobe epilepsy (n=15). Meta-analyses provided estimates by site of stimulation. The RCT using anterior thalamic nucleus DBS will be discussed in the following section.

Two systematic reviews on the use of DBS for drug-resistant epilepsy, both published in 2018, assessed many of the same studies.(34,25) The larger review, by Li et al (2018), identified 10 RCTs and 48 uncontrolled studies.(34) The literature search date was not reported. Meta-analyses were not performed. The largest RCT in which DBS targeted the anterior nucleus of the thalamus, Fisher et al 2010,(36) is described below. Reviewers concluded that more robust clinical trials would be needed.

Randomized Clinical Trials

Trials including 15 patients or more will be described in more detail in this section. Study characteristics are in Table 10 and results are in Table 11. Tables 12 and 13 describe study limitations.

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).(36) Included were 110 patients, ages 18 to 65 years, who experienced at least six 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 three 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 three-month blinded phase; then all patients received unblinded stimulation. 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 10). The publication stated that changes in additional outcome measures did not show significant treatment group differences during the double-blind phase, including 50% responder rates, Liverpool Seizure Severity Scale (LSSS), Quality of Life in Epilepsy (QOLIE-31) scores, but data were not shown. Data for these outcomes are available in the FDA Summary of Safety and Effectiveness (SSED), see Table 10.(37)

Troster et al (2017) assessed neuropsychological adverse events from the SANTE trial during the three-month blinded phase, and at 7-year follow-up during the open-label noncomparative phase (see Table 2).(38) At baseline, there were no differences in depression history between groups. During the three-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 seven-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, one in the control group; p=0.03). At seven-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 9).(39) All patients underwent DBS device implantation, and were followed for six months. Patients were seen weekly to receive the treatment or placebo. To maintain double-blind status, programming was performed by a non-treating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last two months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. Results are summarized in Table 9.

Table 10. Summary of RCT Characteristics for Epilepsy

Study	Country	Sites	Dates	Participants	Interventions	
					Active	Comparator
Fisher et al (2010) Troster et al (2017) SANTE	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)	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 11. Summary of RCT Outcomes for Epilepsy

Study	Seizure Reduction % (p)			Responder (50% or more reduction in seizure frequency)	Hospitalization	Rescue medication (at least one use)	Seizure severity	Quality of life	Adverse Events
	1 Month	2 Months	3 Months						
Fisher et al (2010) Troster et al (2017) SANTE					Mean (SD) annual hospitalizations per patient		Change (SD) in LSSS	Change (SD) in QOLIE-31	
DBS				30% ^a	0.08 (0.56) ^a	22% ^a	-8.2 (17.8) ^a	2.5 (8.7) ^a	
Sham				26% ^a	0.37 (1.17) ^a	22% ^a	-6.8 (19.6) ^a	2.8 (8.0) ^a	
Between-group difference	-11% (NS)	-11% (NS)	-29% (0.002)	p=0.83 ^a	p=0.11 ^a	p=0.87 ^a	p=0.70 ^a	p=0.55 ^a	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)									
Stimulation on	4 seizure free;	-free; 3 responders;	3 responders; 1						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; NS: not statistically significant; SD: standard deviation; LSSS: Liverpool Seizure Severity Scale; QOLIE-31: Quality of Life in Epilepsy Score.

^aNot reported in publication but reported in FDA SSED.

Study limitations are described in Tables 11 and 12. The SANTE study included relevant patients and outcomes and had few design and conduct limitations. Both RCTs were missing report of several important outcomes such as QOL and functional outcomes in the publications although SANTE outcomes are available in the FDA SSED. Cukiert et al (2017) did not include information on power/sample size, flow of participants and missing data.

Table 12. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-up ^e
Fisher et al (2010) SANTE				1. Responder and freedom from seizure, quality of life outcomes not reported in publication; reported in SSED.	
Cukiert et al (2017)				1. Quality of life and Functional outcomes not reported	

SSED: Summary of Safety and Effectiveness.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 13. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^d	Data Completeness ^e	Power ^d	Statistical ^f
Fisher et al (2010) SANTE			2. Several seizure outcomes as well as quality of life collected but not reported in publication; available in SSED.			
Cukiert et al (2017)				2. No mention of how missing diary data or other missing data were handled in analysis. No flow of participants described.	1: No power calculations	2: Not clear if analyses were done independently for each time point or if analyses adjusted for multiple observations 4: Comparative Treatment effects not calculated

SSED: Summary of Safety and Effectiveness.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Observational Studies

Long-term outcomes of the SANTE trial were reported by Salanova et al (2015).⁽⁴⁰⁾ The uncontrolled open-label portion of the trial began after three 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 three-year follow-up, and 83 (75%) completed five 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 five 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 three 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.

A seven year follow-up of SANTE was reported in the FDA SSED.(74) Seventy-three (66% of implanted) patients completed the year 7 visit. Reasons for withdrawals from the study after implantation were: death (6), withdrawal of consent (5), investigator decision (3), therapeutic product ineffective (13), implant site infection or pain (6), other adverse event (7) and elective device removal (1). Fifty patients were included in the year 7 analysis of responder rate; see Table 13. Seventy-four percent of the 50 patients were responders (50% or greater reduction in seizure frequency). QOLIE-31 scores ($n=67$) improved by a mean of 4.9 (SD=11) points at year 7. LSSS scores ($n=67$) improved by a mean of 18 points (SD=23) at year 7. As the FDA documentation notes, interpretation of the long term follow-up is limited by several factors: patients were aware they were receiving DBS, only 66% of implanted patients completed the year 7 visit and those who did not do well may be more likely to leave the study, and changes in anti-epileptic drugs were allowed in long-term follow-up.

Table 14. Seven-Year Outcomes from SANTE^a

Outcomes	Median seizure frequency (change from BL)	Responders ($\geq 50\%$ reduction in seizure frequency)	LSSS, Mean (SD)	QOLIE-31 ≥ 5 point improvement	Hospitalizations, mean (SD) annual number of hospitalizations per patients	Serious device-related adverse event
N	50	50	67	67	80	110
Estimate	-75% ^b	74%	-18.1 (23.5)	43%	0.08 (0.28)	34.5%

LSSS: Liverpool Seizure Severity Scale; QOLIE-31: Quality of Life in Epilepsy Score; SD: standard deviation; BL: baseline.

^a 110 patients were implanted with DBS in SANTE

^b -39% assuming worst case for missing data.

Kim et al (2017) conducted a retrospective chart review of 29 patients with refractory epilepsy treated with DBS.(41) 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 one, 74% at year two, and ranged from 62% to 80% through 11 years of follow-up. Complications included one symptomatic intracranial hemorrhage, one infection requiring removal and reimplantation, and two 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. Many different targets have been investigated and most of the RCTs included fewer than 15 patients. The largest RCT consisted of a three-month blinded phase in which patients were randomized to stimulation or no stimulation targeting the anterior nucleus of the thalamus. After the randomized phase, all patients received stimulation and were followed for 13 additional months. Findings in the first three months were mixed: patients reported significantly fewer seizures in the third month, but not in the first or second month. There were no differences between groups in 50% responder rates, (LSSS, or

(QOoLIE-31 scores. In an uncontrolled follow-up period of the RCT and in many small observational studies, patients reported fewer seizures compared to baseline, however, without a control group, interpretation of results is limited. In addition interpretation of 7-year follow-up of SANTE is limited by high loss to follow-up. Serious adverse events were reported in about one-third of patients. The risk-benefit ratio is uncertain. DBS has not been directly compared to vagus nerve stimulation, another treatment used in patients with drug-refractory epilepsy who are not candidates for resective surgery.

Tourette Syndrome

Clinical Context and Therapy Purpose

Tourette syndrome (TS) is a neurological disorder marked by multiple motor and phonic tics with onset during childhood or early adulthood and which often improve in adulthood. Children with TS frequently have other comorbid conditions such as attention deficit hyperactivity disorder or obsessive-compulsive disorder (OCD).

The question addressed in this evidence review is: Does DBS improve the net health outcome in patients with TS.

The following PICOs were used to select literature to inform this review.

Patients

The population of interest are patients with TS who have disabling tics that are refractory to optimal medical management.

Interventions

The therapy being considered is DBS. Several targets have been investigated such as the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus, STN, caudate nucleus, GPI, and the anterior limb of the internal capsule and nucleus accumbens.

Comparators

Intervention may be initiated when symptoms of TS are disabling or causing difficulty in functioning. Patients may require a therapy to treat tics as well as comorbid attention deficit hyperactivity disorder or OCD. Medication treatment for tics might include antidopaminergic drugs, alpha adrenergic agonists drugs, topiramate or injections of botulinum toxin. Behavioral therapy, primarily based on habit reversal therapy, is also used.

Outcomes

Key efficacy outcomes include measures of motor impairment, tic severity (Yale Global Tic Severity Scale [YGTSS]), functional ability and disability, medication use, and QOL. The overall score for the YGTSS is on a scale from 0 to 100, with lower scores indicating less severe symptoms. It has a motor tic and verbal tick subscale.

Key safety outcomes include death, stroke, depression, cognition, infection and other device and procedure related events.

Study Selection Criteria

1. To assess efficacy outcomes, comparative controlled prospective trials were included, with preference for randomized controlled trials.
2. In the absence of such trials, comparative observational studies, with preference for prospective studies will be included.
3. To assess longer-term outcomes and adverse effects, single arm studies that captured longer periods of follow up and/or larger populations may be included.
4. Studies with duplicative or overlapping populations will be excluded.

Review of Evidence

Systematic Reviews

Several systematic reviews of the literature on DBS for Tourette syndrome have been published.(42-46) 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.(42) 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 four 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 1 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 four 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.

Randomized Controlled Trials

Trials including 15 patients or more will be described in more detail in this section. Study characteristics are shown in Table 15 and results are shown in Table 16. Study limitations are described in Tables 17 and 18.

The crossover RCT was published by Kefalopoulou et al (2015).(47) 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 three months, followed by the opposite phase for the next three 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, two related to surgery and one related to stimulation.

Welter et al (2017) reported results of a sham-controlled RCT of three months of anterior internal globus pallidus (aGPi) DBS in 17 adults with severe TS.(48) The primary endpoint was difference in YGTSS score between the beginning and end of the 3-month double-blind period. The study was powered to detect a benefit amounting to a 30-point reduction in YGTSS score in the active DBS group and may, therefore have been underpowered to detect smaller changes in YGTSS. There was no significant differences in YGTSS score change between groups (active DBS median change 1.1% [IQR –23.9 to 38.1] vs sham DBS median change 0.0% [–10.6 to 4.8]; p=0.39). There was also no difference between groups in change in co-morbid symptoms of OCD, depression or QOL. There were 15 serious adverse events in 13 patients: infections in four patients, one electrode misplacement, one episode of depressive signs, and three episodes of increased tic severity and anxiety.

Table 15. Characteristics of RCTs of DBS for Tourette Syndrome

Study; Trial	Countries	Sites	Dates	Participants ²	Interventions ¹	
					Active	Comparator
Kefalopoulou et al (2015); NCT01647269	UK	2	2009-2013	Adults with TS with chronic and severe tic, with severe Functional impairment (12+ months), had not responded to conventional medical treatment, behavioral intervention had been thought inappropriate or had been unsuccessful	Stimulation on (Bilateral globus pallidus internus [GPi] DBS)	Stimulation off
Welter et al (2017); NCT00478842	France	8	2007-2012	Adults aged 18–60 years with severe, medically refractory TS	N=8 anterior internal globus pallidus (aGPi) DBS	N=9 Sham DBS

DBS: deep brain stimulation; RCT: randomized controlled trial.

Table 16. Results of RCTs of DBS for Tourette Syndrome

Study	Tic Severity	Co-morbid symptoms	Quality of Life	Depression Symptoms	Serious Adverse Events
Kefalopoulou et al (2015)^a	YGTSS, Mean (SD) at 3 months	Y-BOC, Mean (SD) at 3 months	GTS-QOL, Mean (SD) at 3 months	Beck Depression Inventory, Mean (SD) at 3 months	
N	15 ^a	15 ^a	15 ^a	15 ^a	15 ^a
DBS	68.3 (18.6)	12.8 (10.0)	54.3 (28.4)	21.0 (13.8)	3 (20%)
No stimulation	80.7 (12.0)	14.6 (10.3)	62.0 (24.7)	20.5 (14.3)	
Treatment effect (95% CI)	12.4 (0.1–24.7, p=0.05)	p=0.98	p=0.04	p=0.13	
Welter et al (2017)	YGTSS, Mean change (CI) at 3 months	Y-BOC, Mean change (CI) at 3 months	SF-36, Mean change (CI) at 3 months	MADRS, Mean Change at 3 months	
N	16	16	16	16	19
DBS	-4.5 (-12.5 to 0.5)	-3.5 (-6.8 to 0.3)	PCS6.1 (1.2 to 8.7): MCS: 10.1 (1.8 to 16.8):	-2.0 (-6.0 to 0.5)	15 serious adverse events (three in patients who withdrew before stimulation and six each in the active and sham stimulation groups) occurred in 13 patients: infections in four patients, one electrode

misplacement, one episode of depressive signs, and three episodes of increased tic severity and anxiety

No Stimulation	5.0 (-2.5 to 17.5)	0.0 (-1.0 to 0.0)	PCS: -0.4 (-3.1 to 16.1)	0.0 (-2.3 to 1.8)
			MCS: -2.6 (-16.7 to 10.0)	
Treatment effect (95% CI)	p=0.39	p=0.25	PCS:p>0.99	p=0.25
			MCS:p=0.14	

YGTSS: Yale-Brown Obsessive-Compulsive Scale; Gilles de la Tourette Syndrome Quality; MADRS: Montgomery and Asberg Rating Scale of Life (GTS-QOL) scale. Y-BOCS: Yale and Brown Obsessive Compulsive Scale; DBS: deep brain stimulation; CI: confidence interval; SD: standard deviation; RCT: randomized controlled trial; MCS: Mental Component Score; PCS: Physical component Score; SF-36: Short-Form 36 Item Quality of Life Survey.

^a Crossover design

Table 17. Study Relevance Limitations: RCTs of DBS for Tourette Syndrome

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^b	Follow-up ^e
Kefalopoulou et al (2015)					1. 3 months of follow-up
Welter et al (2017)					1. 3 months of follow-up

DBS: deep brain stimulation; RCT: randomized controlled trial.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 18. Study Design and Conduct Limitations: RCTs of DBS for Tourette Syndrome

Study	Allocation ^a	Blinding ^b	Selective Reporting ^d	Data Completeness ^e	Power ^d	Statistical ^f
Kefalopoulou et al (2015)					3. Sample size based on "practical considerations"	
Welter et al (2017)					3. Powered to detect a 30 point reduction in YGTSS in active DBS group	

DBS: deep brain stimulation; RCT: randomized controlled trial; YGTSS: Yale-Brown Obsessive-Compulsive Scale; Gilles de la Tourette Syndrome Quality.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Observational Studies

Martinez-Ramirez et al (2018) reported prospective data from the International Deep Brain Stimulation Database and Registry including 185 consecutive patients with refractory TS who were treated with DBS between 2012 and 2016 at 31 sites in 10 countries in Australia, Europe, Asia and North America. Sixty-four percent of the patients had comorbid OCD and 28% had comorbid attention deficit hyperactivity disorder. The population was 78% male. The mean age at diagnosis was 12 years and mean age at surgery was 29 years. Sixty-seven percent received DBS in the centromedian thalamic region, 25% in the anterior globus pallidus internus, 15% in the posterior globus pallidus internus and 3% in the anterior limb of the internal capsule. The YGTSS score improved from a mean (SD) of 75 (18) at baseline to 41 (20) after 1 year of DBS. More than one-third (35%) of patients had adverse events. Two patients (1.3%) suffered intracranial hemorrhage, 4 (3.2%) had infections, 1 (0.6%) had lead explantation.(49)

Section Summary: Tourette Syndrome

A number of uncontrolled studies, 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. Two RCTs with 15 or more patients have been reported. One RCT found differences in severity of TS for active sham at three months while the other RCT did not. Neither study demonstrated improvements in comorbid symptoms of OCD or depression Both studies reported high rates of serious adverse events.

CLUSTER HEADACHE AND FACIAL PAIN

Clinical Context and Therapy Purpose

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.

The question addressed in this evidence review is: Does DBS improve the net health outcome in patients with cluster headache.

The following PICO's were used to select literature to inform this review.

Patients

The relevant population of interest are patients with cluster headache. The International Headache Society's International Classification of Headache Disorders classifies types of primary and secondary headaches.(50) A summary of cluster headache based on ICHD criteria are below.

Cluster headaches are primary headaches classified as trigeminal autonomic cephalalgias that can be either episodic or chronic. The diagnostic criteria for cluster headaches states that these are attacks of severe, unilateral orbital, supraorbital, and/or temporal pain that lasts 15-180 minutes and occurs from once every other day to eight times a day and further requires for the patient to have had at least 5 such attacks with at least one of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhoea; eyelid oedema; forehead and facial sweating; miosis and/or ptosis, or; a sense of restlessness or agitation. The diagnostic criteria for episodic cluster headache requires at least two cluster periods lasting from seven days to one year if untreated, and

separated by pain-free remission periods of ≥ 3 months. The diagnostic criteria for chronic cluster headache requires cluster headaches occurring for one year or more without remission, or with remission of less than three months. The age at onset for cluster headaches is generally 20-40 years and men are affected three times more often than are women.

Interventions

The therapy being considered is deep brain stimulation.

Comparators

The standard of care treatment to stop or prevent attacks of cluster headache or migraine is medical therapy. Guideline-recommended treatments for acute cluster headache attacks include oxygen inhalation and triptans (e.g., sumatriptan and zolmitriptan). Oxygen is preferred first-line, if available, because there are no documented adverse effects for most adults. Triptans have been associated with primarily nonserious adverse events; some patients experience on ischemic chest pain and distal paresthesia. Use of oxygen may be limited by practical considerations and the FDA-approved labeling for subcutaneous sumatriptan limits use to 2 doses per day. Steroids injections may be used to prevent or reduce the frequency of cluster headaches. Verapamil is also frequently used for prophylaxis although the best evidence supporting its effectiveness is a placebo-controlled RCT including 30 patients.

Given the high placebo response rate in cluster headache, trials with sham DBS are most relevant.

Outcomes

The general outcomes of interest are headache intensity and frequency, the effect on function and quality of life and adverse events.

The most common outcome measures for prevention of cluster headache are decrease in headache days per month compared with baseline and the proportion of responders to the treatment, defined as those patients who report more than a 50%, 75% or 100% decrease in headache days per month compared to pre-treatment.

Key safety outcomes include death, stroke, depression, cognition, infection and other device and procedure related events.

Study Selection Criteria

1. To assess efficacy outcomes, comparative controlled prospective trials were included, with preference for randomized controlled trials.
2. In the absence of such trials, comparative observational studies, with preference for prospective studies will be included.
3. To assess long-term outcomes and adverse effects, single arm studies that captured longer periods of follow-up and/or larger populations may be included.
4. Studies with duplicative or overlapping populations will be excluded.

Review of Evidence

Randomized Controlled Trials

Fontaine et al (2010) published results from a prospective crossover, double-blind, multicenter trial in 11 patients who received DBS of the posterior hypothalamus for severe refractory

chronic cluster headache.(51) The randomized phase compared active with sham stimulation during one-month periods and was followed by a one-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 has published 2 case series (potentially overlapping) on the use of DBS for the ipsilateral posterior hypothalamus in patients with chronic cluster headache.(52,53) 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 three patients who had atypical facial pain.

Section Summary: Cluster Headache and Facial Pain

Several case series and a crossover RCT have been published on the 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.

OTHER NEUROLOGIC AND PSYCHIATRIC DISORDERS

Clinical Context and Therapy Purpose

The role of DBS in treatment of other treatment-resistant neurologic and psychiatric disorders such as 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.

The question addressed in this evidence review is: Does DBS improve the net health outcome in patients with other neurologic and psychiatric disorders.

The following PICOs were used to select literature to inform this review.

Patients

The population of interest are patients with other neurologic and psychiatric disorders such as depression and obsessive-compulsive disorder.

Interventions

The therapy being considered is deep brain stimulation. Several targets have been investigated. Affective limbic structures include the ventral striatum/ventral capsule, anterior limb of the internal capsule, and subgenual cingulate. Memory implicated structures include the fornix and nucleus basalis.

Comparators

Alternative treatments vary by condition. Sham DBS is an appropriate comparator for RCTs.

Outcomes

Key efficacy outcomes include measures of symptoms severity, functional ability and disability, and quality of life.

Outcomes for major depressive disorder are measured with validated scales, most commonly the Hamilton Depression Rating or the Montgomery-Asberg Depression Rating Scale. Response is considered a 50% or greater reduction in symptoms, while remission is based on achieving a specific threshold on one of the scales.

Key safety outcomes include death, stroke, depression, cognition, infection and other device and procedure related events.

Study Selection Criteria

1. To assess efficacy outcomes, comparative controlled prospective trials were included, with preference for randomized controlled trials.
2. In the absence of such trials, comparative observational studies, with preference for prospective studies will be included.
3. To assess long-term outcomes and adverse effects, single arm studies that captured longer periods of follow up and/or larger populations may be included.
4. Studies with duplicative or overlapping populations will be excluded.

TREATMENT-RESISTANT DEPRESSION

Review of Evidence

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.(54) Only three identified studies were controlled with sham stimulation periods, and two 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;(55) this trial is described next.

Controlled Trials

Ventral Capsule/Ventral Striatum

An industry-sponsored, double-blind RCT evaluating DBS of the ventral capsule/ventral striatum in patients with chronic treatment-resistant depression was published by Dougherty et al (2015).(56) The trial included 30 patients with a major depressive episode lasting at least two years and inadequate response to at least four 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 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.

Anterior Limb of the Internal Capsule

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).⁽⁵⁷⁾ 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 four weeks or after the 52-week period ended. At the end of the open-label phase, 10 (40%) patients were classified as responders ($\geq 50\%$ decrease in the Hamilton Depression Rating Scale [HAM-D] score) and 15 (60%) patients were classified as non-responders. 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 non-responders). 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 non-responders (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.

Subcallosal Singulate

Crowell et al (2019) reported long-term follow-up of a within-subject trial with 28 participants with treatment resistant depression or bi-polar II disorder who were treated with deep brain stimulation of the subcallosal cingulate.⁽⁵⁸⁾ Patients were included who had depression for at least 12 months with non-response to at least three antidepressant medications, a psychotherapy trial, and electroconvulsive therapy (lifetime). Seventeen of the patients had a one month sham-controlled period and 11 patients had a one month open label period before the stimulation was turned on. Eight year follow-up was available for 14 of the 28 participants. The primary outcome measure was the Illinois Density Index, which assesses the longitudinal area under the curve for behavioral measures; in this study these included response ($\geq 50\%$ decrease from baseline) and remission (score ≤ 7) on the Hamilton Depression Rating. More than 50% of patients maintained a response and 30% in remission, over the 8 years of follow-up. The physician-rated Clinical Global Impressions severity score improved from 6.1 (severely ill) at baseline to less than three (mildly ill or better) in this open label trial.

Section Summary: Treatment-Resistant Depression

A number of case series and several prospective controlled trials evaluating deep brain stimulation in patients with treatment resistant depression have been published. Two RCTs of deep brain stimulation in the subgenual cingulate cortex and ventral striatum/ventral capsule were terminated for futility. Another RCT of stimulation of the ventral striatum/ventral capsule

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 sham or active stimulation of the anterior limb of the internal capsule 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. A 2019 sham-controlled within-subject study of stimulation of the subcallosal singulate found prolonged response in 50% of patients and remission in 30% of patients with treatment resistant depression. Deep brain stimulation for patients with major depressive disorder who have failed all other treatment options is an active area of research, but brain regions that might be effective for treatment resistant depression have yet to be established.

OBSESSIVE-COMPULSIVE DISORDER

Several systematic reviews evaluating DBS for obsessive-compulsive disorder (OCD) have been published.(59-63) Two of these reviews included meta-analyses pooling study findings. Kisely et al (2014) included only double-blind RCTs of active versus sham DBS.(62) 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 two were only crossover trials. The site of stimulation was the anterior limb of the internal capsule (three studies), the nucleus accumbens (one study), and the STN (one 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 one of the five 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 five 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 one cerebral hemorrhage and two infections requiring electrode removal. Additionally, nonserious transient adverse events were reported, including 13 reports of hypomania, six of increase in depressive or anxious symptoms, and six 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 on the Y-BOCS score.(61) 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 four provided pooled data on percentage of responders (ie, >35% reduction in post treatment 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 one of the five 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.

MULTIPLE SCLEROSIS

Schuurman et al (2008) reported five-year follow-up of 68 patients comparing thalamic stimulation and thalamotomy for multiple indications included 10 patients with MS.(2) Trial details are discussed with essential tremor in the 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 ten MS patients provides insufficient data for drawing conclusions on the efficacy of DBS for this population.

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 five to six 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 of 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 Gi or STN have consistently demonstrated clinically significant improvements in outcomes (eg, neurologic function). Other systematic reviews also found significantly better outcomes after DBS than after a control intervention. An RCT in patients with levodopa-responsive Parkinson disease of at least four years of duration and uncontrolled motor symptoms found that quality of life at two 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 one type of stimulation was 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 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 improvement in motor scores and disability scores after six months and last follow-up (mean, 32 months). Both double-blind RCTs 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 an RCT and case series. 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). The RCT did not report statistically significant improvement in the dystonia severity outcomes or the secondary outcomes related to disability and QOL but may have been under-powered. 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 systematic reviews, RCTs and many observational studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Two RCTs with more than 15 patients were identified; The larger RCT evaluated anterior thalamic nucleus DBS and reported that DBS had a positive impact on seizure frequency during some parts of the blinded trial phase but not others, and a substantial number of adverse events (in >30% of patients). There were no differences between groups in 50% responder rates, Liverpool Seizure Severity Scale, or Quality of Life in Epilepsy scores. A seven year open-label follow-up of the RCT included 66% of implanted patients; reasons for missing data were primarily related to adverse events or dissatisfaction with the device. Reduction in seizure frequency continued to improve during follow-up among the patients who continued follow-up. 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 the net health outcome. 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 observational studies, RCTs and systematic reviews. The relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Two RCTs with 15 or more patients have been reported. One RCT found differences in severity of TS for active versus sham at three months while the other RCT did not. Neither study demonstrated improvements in comorbid symptoms of OCD or depression. Both studies reported high rates of serious adverse events. 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. The relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. In the

randomized study, the between-group difference in response 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. A number of case series and several prospective controlled trials evaluating deep brain stimulation in patients with have been published. Two RCTs of deep brain stimulation in the subgenual cingulate cortex and ventral striatum/ventral capsule were terminated for futility. Another RCT of stimulation of the same brain area (ventral striatum/ventral capsule) 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 sham or active stimulation of the anterior limb of the internal capsule 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. Stimulation of the subcallosal (subgenual) cingulate was evaluated in a 2019 sham-controlled within-subject study that found prolonged response in 50% of patients and remission in 30% of patients with treatment resistant depression. Deep brain stimulation for patients with major depressive disorder who have failed all other treatment options is an active area of research, but the brain regions that might prove to be effective for treatment resistant depression have yet to be established. 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. The 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 outcomes.

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

Supplemental Information

CLINICAL INPUT RECEIVED 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, the Blue Cross Blue Shield Association received input from two academic medical centers and two physician specialty societies while its policy was under review in 2014. Input supported the use of bilateral DBS in patients with medically unresponsive tremor in both limbs.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Neurology

Essential Tremor

The American Academy of Neurology (AAN) (2011) updated its guidelines on the treatment of essential tremor (ET).(64) This update did not change the conclusions and recommendations of the AAN (2005) practice parameters on DBS for ET.(65) 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 guidelines from the AAN (2006) on the treatment of Parkinson disease (PD) with motor fluctuations and dyskinesia found that, although the criteria are evolving, patients with PD considered candidates for DBS include those who are levodopa-responsive, nondemented, and neuro-psychiatrically intact patients who have intractable motor fluctuations, dyskinesia, or tremor.(66) The 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 guidelines from AAN (2010) on the treatment of nonmotor symptoms of PD found insufficient evidence for the treatment of urinary incontinence with DBS of the STN.(67) The 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 guidelines (57) from the AAN (2013) on the treatment of tardive syndromes were updated in 2018.(68) 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).

Tourette Syndrome

Guidelines from AAN (2019) provide recommendations on the assessment for and use of deep brain stimulation in adults with severe, treatment-refractory tics.(69) AAN notes that patients with severe Tourette syndrome resistant to medical and behavioral therapy may benefit from deep brain stimulation, but there is no consensus on the optimal brain target. Brain regions that have been stimulated in patients with Tourette Syndrome include the centromedian thalamus, the globus pallidus internus (ventral and dorsal), the globus pallidus externus, the subthalamic nucleus, and the ventral striatum/ventral capsular nucleus accumbens region. AAN concludes that deep brain stimulation of the anteromedial globus pallidus is possibly more likely than sham stimulation to reduce tic severity.

American Society for Stereotactic and Functional Neurosurgery et al

The American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (2014) published a joint systematic review and guidelines on DBS for obsessive-compulsive disorder.(60) The document concluded that there was a single level I study supporting the use of bilateral STN DBS for medically refractory obsessive-compulsive disorder and a single level II study supporting bilateral nucleus accumbens DBS for medically refractory obsessive-compulsive disorder. It also concluded that the evidence on unilateral DBS was insufficient.

Congress of Neurologic Surgeons

In 2018, evidence-based guidelines from the Congress of Neurologic Surgeons compared the efficacy of bi-lateral deep brain stimulation of the subthalamic nucleus and globus pallidus internus for the treatment of patients with Parkinson disease.(70)

Table 19. Recommendations of the Congress of Neurologic Surgeons for DBS for Parkinson Disease

Goal	Most Effective Area of Stimulation (subthalamic nucleus or globus pallidus internus)	Level of Evidence
Improving motor symptoms	subthalamic nucleus or globus pallidus internus are similarly effective	I
Reduction of dopaminergic medication	subthalamic nucleus	I
Treatment of "on" medication dyskinesias	globus pallidus internus if reduction of medication is not anticipated	I
Quality of life	no evidence to recommend one over the other	I
Lessen impact of DBS on cognitive decline	globus pallidus internus	I
Reduce risk of depression	globus pallidus internus	I
Reduce adverse effects	insufficient evidence to recommend one over the other	Insufficient

DBS: Deep brain stimulation

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

The NICE (2006) made the same statements about the use of DBS for treatment of both tremor and dystonia.(71) 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 guidance from NICE (2011) indicated there is evidence that DBS for refractory chronic pain (excluding headache) is associated with serious risks (72) 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 Cephalgia's

The guidance from NICE (2011) indicated that the evidence on the efficacy of DBS for intractable trigeminal autonomic cephalgias (eg, cluster headaches) was “limited and inconsistent, and the evidence on safety showed that there were serious but well-known adverse effects.”(73)

Refractory Epilepsy

The guidance from NICE (2012) indicated that the evidence on the efficacy of DBS for refractory epilepsy was limited in both quantity and quality: The evidence on safety shows that there are serious but well-known adverse effects.(74)

Parkinson's Disease

The NICE (2003) stated the evidence on the safety and efficacy of DBS for treatment of Parkinson disease “appears adequate to support the use of the procedure.”(75) 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

Table 20. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
ONGOING			
Epilepsy			
NCT01521754 ^a	Product Surveillance Registry- Deep Brain Stimulation for Epilepsy	191	Mar 2020
NCT02076698	Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy	62	Jun 2021
NCT04181229	Deep Brain Stimulation Post Failed Vagal Nerve Stimulation	50	Nov 2022
NCT04164056	Hippocampal and Thalamic deep brain stimulation for Bilateral Temporal Lobe Epilepsy	80	Sep 2024
NCT03900468 ^a	Medtronic Deep Brain Stimulation Therapy for Epilepsy Post-Approval Study (EPAS)	216	Mar 2027

Huntington's Disease				
NCT02535884a	Deep Brain Stimulation of the Globus Pallidus (GP) in Huntington's Disease	50		Oct 2020
Parkinson Disease				
NCT02937688 ^a	Deep Brain Stimulation for Parkinson's Disease International Study (REACH-PD)	264		Apr 2021
NCT00354133	The Effect of Deep Brain Stimulation of the Subthalamic Nucleus on Quality of Life in Comparison to Best Medical Treatment in Patients With Complicated Parkinson's Disease and Preserved Psychosocial Competence (EARLYSTIM-study)	251		Mar 2022
NCT01839396 ^a	Implantable Neurostimulator for the Treatment of Parkinson's Disease (INTREPID)	313		Aug 2023
Obsessive-Compulsive Disorder				
NCT01506206	ON/OFF Stimulation and Impulsivity in Patients With Deep Brain Stimulators	60		Dec 2020
NCT01590862	ON/OFF Stimulation and Reward Motivation in Patients With Deep Brain Stimulators	60		Dec 2020
NCT00640133	Effectiveness of Deep Brain Stimulation for Treating People With Treatment Resistant Obsessive-Compulsive Disorder	27		Aug 2020
NCT02773082 ^a	Reclaim Deep Brain Stimulation Therapy for Obsessive-Compulsive Disorder (OCD)	50		Apr 2020
NCT04228744	The Efficacy and Mechanism of deep brain stimulation in VIC and NAcc for Refractory OCD	20		Dec 2022
NCT02844049	European Study of Quality of Life in Resistant OCD Patients Treated by subthalamic nucleus deep brain stimulation	60		Dec 2023
Treatment Resistant Depression				
NCT03653858 ^a	Controlled Randomized Clinical Trial to Assess Efficacy of Deep Brain Stimulation of the sIMFB in Patients With Treatment Resistant Major Depression (FORSEIII)	47		Jun 2023
NCT01984710	Deep brain stimulation for treatment resistant depression Medtronic Activa PC+S	20		Sep 2023
NCT00367003	Deep Brain Stimulation for Treatment Resistant Depression	40		Nov 2024
UNPUBLISHED				
NCT01801319	A Clinical Evaluation of Subcallosal Cingulate Gyrus Deep Brain Stimulation for Treatment-Resistant Depression	40		Dec 2017 (status unknown)
NCT01329133	Deep Brain Stimulation and Obsessive-Compulsive Disorder (STOC2)	31		Apr 2019 (completed)
NCT01973478	Deep Brain Stimulation in Patients With Chronic Treatment Resistant Depression	9 enrolled		Jan 2020 (suspended)

NCT: national clinical trial

^a Denotes industry-sponsored or cosponsored trial

Government Regulations

National:

CMS has a National Coverage Determination (NCD) for Deep Brain Stimulation for Essential Tremor and Parkinson's Disease (160.24):

Effective for services furnished on or after April 1, 2003, Medicare will cover unilateral or bilateral thalamic ventralis intermedialis nucleus (VIM) deep brain stimulation (DBS) for the

treatment of essential tremor (ET) and/or parkinsonian tremor and unilateral or bilateral subthalamic nucleus (STN) or globus pallidus interna (GPi) DBS for the treatment of Parkinson's disease (PD) when the following conditions are met.(66)

1. DBS devices must be U.S. Food and Drug Administration (FDA) approved devices for DBS or devices used in accordance with FDA-approved protocols governing Category B Investigational Device Exemption (IDE) DBS clinical trials.
2. For thalamic VIM DBS, patients must meet all of the following criteria:
 - a) Diagnosis of ET based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor-dominant form.
 - b) Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.
 - c) Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.
3. For STN or GPi DBS, patients must meet all of the following criteria:
 - a) Diagnosis of PD based on the presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia).
 - b) Advanced idiopathic PD as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.
 - c) L-dopa responsive with clearly defined "on" periods.
 - d) Persistent disabling Parkinson's symptoms or drug side effects (e.g., dyskinesias, motor fluctuations, or disabling "off" periods) despite optimal medical therapy.
 - e) Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings

DBS is not is not covered for ET or PD patients with any of the following:

1. Non-idiopathic Parkinson's disease or "Parkinson's Plus" syndromes.
2. Cognitive impairment, dementia or depression, which would be worsened by or would interfere with the patient's ability to benefit from DBS.
3. Current psychosis, alcohol abuse or other drug abuse.
4. Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.
5. Previous movement disorder surgery within the affected basal ganglion.
6. Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation.

Local:

There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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* 2008; 23(8):1146-53.
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* 2008; 79(6):694-9.
4. Putzke JD, Uitti RJ, Obwegeser AA et al. Bilateral thalamic deep brain stimulation: midline tremor control. *J Neurol Neurosurg Psychiatry* 2005; 76(5):684-90.
5. Pahwa R, Lyons KE, Wilkinson SB et al. Long-term evaluation of deep brain stimulation of the thalamus. *J Neurosurg* 2006; 104(4):506-12.
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* 2006; 21 Suppl 14:S290-304.
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* 2007; 22(12):1722-8.
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.
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*. 2016;11:777- 786.
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*.2016;11(6):e0156721.
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-analysis of randomized controlled trials. *Sci Rep*. May 04 2016;6:25285.
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*. 2016;12:1435-1444.
21. Wong JK, Cauraugh JH, Ho KWD et al. STN vs. GPi deep brain stimulation for tremor suppression in Parkinson disease: A systematic review and meta-analysis. *Parkinsonism Relat. Disord*. 2019 Jan;58:56-62. PMID 30177491
22. U.S. Food and Drug Administration. Summary of Safety and Probable Benefit. Medtronic Activa Dystonia Therapy. 2003; retrieved March 20, 2020 from: http://www.accessdata.fda.gov/cdrh_docs/pdf2/H020007b.pdf.
23. 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.
24. Rodrigues, FF, Duarte, GG, Prescott, DD, Ferreira, JJ, Costa, JJ. Deep brain stimulation for dystonia. *Cochrane Database Syst Rev*, 2019 Jan 11;1:CD012405. PMID 30629283.
25. Kupsch, AA, Benecke, RR, Müller, JJ, et al., Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N. Engl. J. Med.*, 2006 Nov 10;355(19). PMID 17093249.
26. 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
27. Gruber, DD, Südmeyer, MM, Deuschl, GG, et al., Neurostimulation in tardive dystonia/dyskinesia: A delayed start, sham stimulation-controlled randomized trial. *Brain Stimul*, 2018;11(6). PMID 30249417.
28. Damier P, Thobois S, Witjas T et al. Bilateral deep brain stimulation of the globus pallidus to treat tardive dyskinesia. *Arch Gen Psychiatry* 2007; 64(2):170-6.
29. Gruber D, Trottenberg T, Kivi A et al. Long-term effects of pallidal deep brain stimulation in tardive dystonia. *Neurology* 2009; 73(1):53-8.
30. 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
31. Kwan, PP, Arzimanoglou, AA, Berg, AA, et al., Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*, 2009 Nov 6;51(6). PMID 19889013.
32. Borghs, SS, de la Loge, CC, Cramer, JJ. Defining minimally important change in QOLIE-31 scores: estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. *Epilepsy Behav*, 2012 Feb 22;23(3). PMID 22341962.
33. Sprengers, MM, Vonck, KK, Carrette, EE, Marson, AA, Boon, PP. Deep brain and cortical stimulation for epilepsy. *Cochrane Database Syst Rev*, 2017 Jul 19;7:CD008497. PMID 28718878.
34. Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. *Epilepsia*. Feb 2018;59(2):273-290. PMID 29218702

35. 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
36. Fisher R, Salanova V, Witt T et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010; 51(5):899-908.
37. Food and Drug Administration. Medtronic DBS System for Epilepsy, Summary of Safety and Effectiveness Data (SSED). March 20, 2020. PMA P960009/S219.
38. 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
39. 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
40. 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
41. 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
42. Baldermann JC, Schuller T, Huys D, et al. Deep Brain Stimulation for Tourette-Syndrome: A Systematic Review and Meta-Analysis. *Brain Stimul.* Dec 29 2015. PMID 26827109
43. Frait A, Pal G. Deep Brain Stimulation in Tourette's Syndrome. *Front Neurol.* 2015;6:170. PMID 26300844
44. 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
45. Servello D, Zekaj E, Saleh C, et al. 16 years of Deep Brain Stimulation in Tourette's Syndrome: a critical review. *J Neurosurg Sci.* Jan 20 2016. PMID 26788742
46. 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* 2012.
47. 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
48. Welter, MM, Houeto, JJ, Thobois, SS, et al., Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. *Lancet Neurol,* 2017 Jun 25;16(8). PMID 28645853.
49. Martinez-Ramirez, DD, Jimenez-Shahed, JJ, Leckman, et al., Efficacy and Safety of Deep Brain Stimulation in Tourette Syndrome: The International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. *JAMA Neurol,* 2018 Jan 18;75(3). PMID 29340590.
50. International Headache Society. International Classification of Headache Disorders. 2018; <https://www.ichd-3.org>. Accessed March 20, 2020.
51. 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* 2010; 11(1):23-31.
52. Bussone G, Franzini A, Proietti Cecchini A et al. Deep brain stimulation in craniofacial pain: seven years' experience. *Neurol Sci* 2007; 28 Suppl 2:S146-9.

53. 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* 2007; 28 Suppl 2:S138-45.
54. Morishita T, Fayad SM, Higuchi MA et al. Deep Brain Stimulation for Treatment-resistant Depression: Systematic Review of Clinical Outcomes. *Neurotherapeutics* 2014.
55. 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
56. 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
57. 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.
58. Crowell AL, Riva-Posse P, Holtzheimer PE, et al. Long-Term Outcomes of Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression. *Am J Psychiatry*. Nov 01 2019; 176(11): 949-956. PMID 31581800
59. de Koning PP, Figeo 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* 2011; 13(4):274-82.
60. 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
61. 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*. 2015;10(7):e0133591. PMID 26208305
62. 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
63. 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.
64. Zesiewicz TA, Elble R, Louis ED et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2005; 64(12):2008-20. PMID 15972843
65. 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* 2006; 66(7):983-95. PMID 16606909
66. Zesiewicz TA, Sullivan KL, Arnulf I et al. Practice Parameter: treatment of nonmotor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2010; 74(11):924-31. PMID 20231670
67. Bhidayasiri R, Jitkrisadakul 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
68. Pringsheim T, Okun MS, Muller-Vahl K, et al. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*. May 07 2019; 92(19): 896-906. PMID31061208

69. Rughani A, Schwalb JM, Sidiropoulos C, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation for the Treatment of Patients With Parkinson's Disease: Executive Summary. *Neurosurgery*. Jun 01 2018; 82(6): 753-756.PMID 29538685
70. National Institute for Health and Care Excellence (NICE). Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) [IPG188]. 2006; retrieved March 20, 2020 from: <https://www.nice.org.uk/guidance/ipg188>.
71. National Institute for Health and Care Excellence (NICE). Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) [IPG188]. 2006; retrieved March 20, 2020 from: <https://www.nice.org.uk/guidance/ipg188>.
72. National Institute for Health and Care Excellence (NICE). Deep brain stimulation for refractory chronic pain syndromes (excluding headache) [IPG382]. 2011; retrieved March 20, 2020 from: <http://guidance.nice.org.uk/IPG382>.
73. National Institute for Health and Care Excellence (NICE). Deep brain stimulation for intractable trigeminal autonomic cephalalgias [IPG381]. 2011; retrieved March 20, 2020 from: <http://www.nice.org.uk/IPG381>.
74. National Institute for Health and Care Excellence (NICE). Deep brain stimulation for refractory epilepsy [IPG416].2012; retrieved March 20, 2020 from: <http://guidance.nice.org.uk/IPG416>.
75. National Institute for Health and Care Excellence (NICE). Deep brain stimulation for Parkinson's disease [IPG19].2003; retrieved March 20, 2020 from: <https://www.nice.org.uk/guidance/ipg19>.
76. Centers for Medicare & Medicaid (CMS). National Coverage Determination (NCD) for Deep Brain Stimulation for Essential Tremor and Parkinson's Disease (160.24). 2003; retrieved March 20, 2020 from: <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?ncdid=279&ncdver=1&keyword=deep%20brain%20stimulation&keywordType=starts&areald=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAA&KeyWordLookUp=Doc&KeyWordSearchType=Exact>.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 10/27/20, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
6/3/02	6/3/02	7/2/02	Joint policy established
9/27/03	9/27/03	10/14/03	Routine maintenance
2/28/05	2/28/05	2/28/05	Routine maintenance
11/1/06	8/30/06	10/29/06	Routine maintenance
11/1/07	8/21/07	10/27/07	Routine maintenance
1/1/09	10/13/08	12/30/08	Routine maintenance, MS added as investigational, new codes added
9/1/10	6/15/10	6/15/10	Routine maintenance
3/1/12	12/13/11	12/21/11	Extensive changes to Description/Background section; Medical Policy statement revised; Inclusions/exclusions revised to reflect policy position changes; Rationale section and references updated
5/1/13	2/19/13	3/4/13	Routine maintenance; Rationale section and references updated; title shortened to "Deep Brain Stimulation"
3/1/15	12/9/14	12/29/14	Routine maintenance; added bilateral deep brain stimulation of the thalamus as an inclusion; added Alzheimer disease, anorexia nervosa, alcohol addiction, and chronic pain to the list of exclusions; references and rationale updated
7/15/16	4/19/16	4/19/16	Routine approval
9/1/16	6/21/16	6/21/16	Routine maintenance
9/1/17	6/20/17	6/20/17	<ul style="list-style-type: none"> • Routine maintenance • Inclusions updated for unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus to include the statement "OR Parkinson Disease for at least 4 years" per FDA approval. • Inclusion bullet added "essential tumors"

9/1/18	6/19/18	6/19/18	<ul style="list-style-type: none"> • Routine maintenance • Added “upper” to second policy statement
9/1/19	6/18/19	6/18/19	Routine maintenance
3/1/20	12/17/19		<ul style="list-style-type: none"> • Routine maintenance • Literature review r/t DBS for epilepsy
3/1/21	12/15/20		<ul style="list-style-type: none"> • Routine maintenance

Next Review Date: 4th Qtr, 2021

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: 11/05/01	Revised: N/A
BCBSM: 6/03/02	Revised: N/A

**BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: DEEP BRAIN STIMULATION**

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.