Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/24**
(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 (i.e., 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 approved by the U.S. Food and Drug Administration (FDA) through the pre-market approval process 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-S219). Other deep brain stimulation systems are described in Table 1.

Table 1. Deep Brain Stimulation Systems

System	Manufacturer	FDA Product Code	PMA or HDE	Approval Date	Indications
Activa® Deep Brain Stimulation Therapy System	Medtronic	MBX	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		H050003	2009	Bilateral stimulation of the anterior limb of the internal capsule for severe obsessive-compulsive disorder
Brio Neurostimulation System	St. Jude Medical	NHL	P140009	2015	Parkinsonian tremor (subthalamic nucleus) and essential tremor (thalamus)
Infinity DBS	Abbott Medical/St. Jude Medical	PJS	P140009	2016	Parkinsonian tremor
Vercise DBS System	Boston Scientific	NHL	P150031	2017	Moderate-to-advanced levodopa-responsive PD inadequately controlled with medication alone
Medtronic DBS System for Epilepsy	Medtronic	MBX	P960009-S219	2018	Expanded indication for epilepsy with bilateral stimulation of the anterior nucleus of the thalamus
Precept PC Deep Brain Stimulation	Medtronic	MHY	P960009-S	2020	Records brain signals while delivering therapy for PD or primary dystonia
Vercise Genus DBS System	Boston Scientific NHL	NHL	P150031-S034	2021	Stimulation of the subthalamic nucleus and globus pallidus for PD
SenSight Directional Lead System	Medtronic	MHY	P960009	2021	Unilateral or bilateral stimulation for PD, tremor, dystonia, and epilepsy

DBS: deep brain stimulation; HDE: humanitarian device exemption; PD: Parkinson disease; PMA: premarket approval

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 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, multiple sclerosis, 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

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

Bilateral deep brain stimulation of the thalamus may be indicated in individuals 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 individuals:

- 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

- Individuals 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 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, multiple sclerosis, 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

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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 (i.e., “on” state) and the nadir response during drug troughs (i.e., “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.

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

Observational Studies

Putzke et al (2005) reported on a series of 25 patients with ET treated with bilateral DBS for management of midline tremor (head, voice, tongue, trunk).(4) Three patients died of unrelated causes, 1 patient was lost to follow-up due to transfer of care, and 1 patient did not have baseline evaluation; these patients were not included in the analysis. Patients were evaluated at baseline (before implantation of second stimulator), and at 1, 3, 6, 12, 24, and 36 months. At 12 months, evaluations were obtained from 76% of patients; at 36 months, 50% of patients were evaluated. The most consistent improvement on the Tremor Rating Scale during both unilateral and bilateral stimulation was found for head and voice tremor. The incremental improvement over unilateral stimulation through the first 12 months of bilateral stimulation was significant ($p<0.01$). For bilateral stimulation at months 3 and 12, outcome measures were significantly better than unilateral stimulation at month three ($p<0.05$). Limited sample size precludes interpretation 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 8 had bilateral implantation.(5) Sixteen patients with unilateral and 7 with bilateral stimulators completed at least part of the 5-year follow-up evaluations. Patients with bilateral stimulation had a 78% improvement in mean motor tremor scores in the stimulation on state compared with baseline

at 5-year follow-up (p=0.02) and 36% improvement in activities of daily living (ADL) scores. Patients with unilateral stimulation improved by 46% on motor tremor scores and 51% on ADL scores (p<0.01). Stimulation-related adverse events were reported in more than 10% of patients with unilateral and bilateral thalamic stimulators. Most were mild and were reduced with changes in stimulation parameters. Adverse events in patients with bilateral stimulation (eg, dysarthria and other speech difficulties, disequilibrium or balance difficulties, abnormal gait) persisted, despite optimization of the stimulation parameters.

Directional Deep Brain Stimulation

Randomized Controlled Trial

Three new DBS systems with directional leads are currently available (approved by the Food and Drug Administration [FDA] in 2016, 2017, and 2021). Directional leads potentially enable clinicians to target more specific areas of the brain to be treated with the direct current. Schnitzler et al (2022) conducted a prospective crossover study with randomized, double-blind endpoint evaluation in 234 patients with Parkinson disease.(29) All patients received conventional deep brain stimulation for 3 months followed by directional deep brain stimulation for 3 months. The therapeutic window was wider after using directional stimulation in 90.6% of patients, with a mean increase of 41% compared to conventional deep brain stimulation.

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 PARKINSON DISEASE

Review of Evidence

Advanced Parkinson Disease

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 was both statistically significant and clinically meaningful.

- The beneficial treatment effect lasted at least for the 6 to 12 months observed in most trials. While there was limited 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.

Systematic Reviews

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.

Parkinson Disease 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 4 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 2 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 3 secondary outcomes were assessed using UPDRS subscales. Regarding medication use, the levodopa-equivalent daily dose was reduced by 39% in the DBS plus medical therapy group and increased by 21% in the medical therapy only group.

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

Globus Pallidus Interna versus Subthalamic Nucleus Stimulation

Systematic Reviews

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-simulation state (5 studies; MD = -1.39; 95% CI, -3.70 to 0.92) or the on-medication/on-stimulation state (5 studies; MD = -0.37; 95% CI, -2.48 to 1.73). At the 12- and 24-month follow-ups, only 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 Parkinson disease.

Section Summary: Symptoms Associated with Parkinson Disease

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.

PRIMARY 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.

Review of Evidence

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 (Kupschetl 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 2 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 3 months.(25) 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 9months of the open-label extension period. During the study, 7 patients experienced dysarthria (i.e., 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 et al (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
Volkmann et al (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 et al (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)	
Volkmann et al	**Change in**	**Change in TWSTRS**	**Change in SF-**	**Change in BDI at**	

(2014)	TWSTRS severity at 3 months	disability at 3 months	36 at 3 months	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 stimulation, 4 related to dystonia
Sham	-1.3 (2.4)	-1.8 (3.8)	PCS: 3.6 (19.2) MCS: 8.9 (14.4)	-0.4 (3.7)	
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 et al (2006)					1: Only 3 months of double-blind study
Volkmann et al (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 et al (2006)			1: Registered after enrollment was complete			
Volkmann et al (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

Systematic Review

Grabel et al (2023) conducted a systematic review and meta-analysis of pallidal deep brain stimulation for tardive dystonia (Tables 6 and 7).(69) A total of 14 articles (observational studies, randomized studies, or case reports) that described use of deep brain stimulation to the globus pallidus pars interna and assessed efficacy using the Burke-Fahn-Marsden Dystonia Rating Scale were included. There was a risk of publication bias among the included studies (p=.0009). The 134 patients ranged in age from 11 to 77 years and had a history of tardive dystonia for 0.5 to 46 years. Table 8 summarizes the results of the analysis. A mixed effects model with no covariates reported a mean improvement in dystonia score of 66.88% (95% CI, 57.46% to 68.63%).Including covariates in the model (follow-up duration, year, and baseline Burke-Fahn-Marsden Dystonia Rating Scale score) increased the estimated improvement to 72.66%. Fixed effects and random effects models had similar estimated improvement (63.1% and 70.56%, respectively).

Table 6. Systematic Review Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Grabel et al (2023)	until 2021	14	Patients who received DBS to the globus pallidus pars interna for TD	134 (2 to 22)	RCT, observational studies, and case reports	0.03 to 53 months

DBS: deep brain stimulation; RCT: randomized controlled trial; TD: tardive dystonia.

Table 7. Systematic Review Results

Study	BFMDRS, mean (SD)
Grabel et al (2023)	
N	134
Overall estimate of improvement, % (mixed effects model)	66.88 (11.96)

BFMDRS: Burke-Fahn-Marsden-Dystonia-Rating-Scale; CI: confidence interval; SD, standard deviation

Randomized Controlled Trials

One RCT evaluated efficacy of pallidal DBS in patients with tardive dystonia. Characteristics are shown in Table 6 and results are in Table 7. Briefly, 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 10 and 11.

Table 8. Characteristics of RCTs of DBS for Tardive Dyskinesia and Tardive Dystonia

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
					Active	Comparator
Gruber 2018; NCT00331669	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 medical treatment	N=12 Pallidal DBS	N=13 Sham

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

Table 9. 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% CI)	p=0.72	p=0.43	PCS: p=0.17 MCS: p=0.53	p=0.69	

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 10. 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 11. 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.

Observational Studies

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.

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 Extrapyramidal Symptoms Rating Scale (ESRS). At 12 months, the mean decrease in ESRS score was 58% (range, 21% to 81%).

Section Summary: Tardive Dyskinesia and Tardive Dystonia
Evidence for the use of deep brain stimulation to treat tardive syndromes consists of a systematic review, an RCT with 3 months of blinded follow-up and case series with follow-up of 6 months to approximately 4 years. The systematic review found an improvement in symptom severity with deep brain stimulation, but the authors noted some cases of symptom worsening or lack of improvement. The RCT did not report statistically significant improvement in the dystonia severity outcomes or the secondary outcomes related to disability and quality of life for deep brain stimulation compared to sham, but the study did not recruit the number of patients for which it was originally powered.

DRUG-REFRACTORY EPILEPSY

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.(34,35) 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 are described in more detail in this section. Study characteristics are in Table 12 and results are in Table 13. Tables 13 and 14 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).(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 12). 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 12.(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 11).(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 11).(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 11.

Table 12. 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 13. 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		Mean (SD) annual hospitalizations per patient		Change (SD) in LSSS	Change (SD) in QOLIE-31	
Fisher et al (2010) Troster et al (2017									

SANTE									
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; 3 responders; 1 no response								2 patients with local skin erosions at cranial site of implant, treated with antibiotics
Stimulation off	0 seizure-free; 3 responders; 5 no response								

FIAS: focal impaired awareness seizure; RCT: randomized controlled trial; NS: not statistically significant; SD: standard deviation; LSSS: Liverpool Seizure Severity Scale; QOLIE-31: Quality of Life in Epilepsy Score.
[a]Not reported in publication but reported in FDA SSED.

Study limitations are described in Tables 14 and 15. The SANTE study included relevant patients and outcomes and had few design and conduct limitations. Both publications did not report several important outcomes such as QOL and functional outcomes, although SANTE outcomes are available in the FDA Summary of Safety and Effectiveness. Cukiert et al (2017) did not include information on power/sample size, flow of participants and missing data.(39)

Table 14. 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 15. 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 3 months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician's discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the 3-year follow-up, and 83 (75%) completed 5 years. Among patients with at least 70 days of diary entries, the median change in seizure frequency from baseline was 41% at 1 year and 69% at 5 years ($p<0.001$ for both). During the trial, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first months after implantation. They included implant-site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the trial and none was considered to be device related. Depression was reported in 41 (37%) patients following implant; in 3 cases, it was considered device related. Memory impairment (nonserious) was reported in 30 (27%) patients during the trial, half of whom had a history of the condition.

A 7-year follow-up of SANTE was reported in the FDA SSED (Table 16).(37) 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 12. 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 16. Seven-Year Outcomes from SANTE[a]

Outcomes	Median seizure frequency (change from BL)	Responders (≥ 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 2, 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 2 lead disconnections.

Section Summary: Drug-Refractory 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 3-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 3 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 multiple 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).

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 (i.e., those published in 2015 to 2017) qualitatively described the literature.

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.

Wehmeyer et al (2021) also conducted a pooled analysis.(75) A total of 65 studies with 376 patients were included; the primary outcome was YGTSS scores and scores were significantly reduced at maximum follow-up of median 25 months (p<.001). The median scores decreased from 79.92 points (interquartile range [IQR], 13.25) to 34.69 points (IQR, 20.93) post-surgery, which represented a reduction rate of 56.59%. A majority of patients (69.4%) also experienced symptom reduction of more than 50% at maximum follow-up. In addition, other tic-related outcome measures (modified Rush video-based tic rating scale, YGTSS total tic score) and comorbidities (Yale-Brown Obsessive Compulsive Scale, Becks Depression Inventory), were also significantly reduced after deep brain stimulation.

Randomized Controlled Trials
Trials including 15 patients or more will be described in more detail in this section. Study characteristics are shown in Table 17 and results are shown in Table 18. Study limitations are described in Tables 19 and 20.

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 3 months, followed by the opposite phase for the next 3 months. Of the 15-receiving surgery, 14 were randomized and 13 completed assessments after both on and off phases. For the 13 trial completers, mean YGTSS scores were 80.7 in the off-stimulation phase and 68.3 in the on-stimulation phase. The mean difference in YGTSS scores indicated an improvement of 12.4 points (95% CI, 0.1 to 24.7 points), which was statistically significant (p=0.048) after Bonferroni correction. There was no significant between-group difference in YGTSS scores for patients randomized to the on-stimulation phase first or second. Three serious adverse events were reported, two related to surgery and one related to stimulation.

Welter et al (2017) reported results of a sham-controlled RCT of 3 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 were 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 4 patients, one electrode misplacement, 1 episode of depressive signs, and three episodes of increased tic severity and anxiety.

Table 17. 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 Tourette Syndrome 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 18. 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) MCS: –2.6 (–16.7 to 10.0)	0.0 (–2.3 to 1.8)	
Treatment effect (95% CI)	p=0.39	p=0.25	PCS:p>0.99 MCS:p=0.14	p=0.25	

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 19. Study Relevance Limitations: RCTs of DBS for Tourette Syndrome

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[b]	Follow-up[e]
Kefalpoulou 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 20. 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 Tourette syndrome 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. Fifty-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 less than 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 3 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

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.

Observational Studies
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 to 26 months of follow-up) without significant adverse events in 16 patients with chronic cluster headaches and in 1 patient with neuralgiform headache; treatment failed in the 3 patients who had atypical facial pain.

Section Summary: Cluster Headache and Facial Pain
Several case series and a crossover RCT have been published on 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.

TREATMENT-RESISTANT DEPRESSION

Review of Evidence

Systematic Reviews
A variety of target areas are being investigated for use of deep brain stimulation for treatment-resistant depression. Sobstyl et al (2022) published a systematic review of studies that evaluated deep brain stimulation to the subcallosal cingulate cortex in patients with treatment resistant depression.(70) All study designs were considered but at least 5 patients were required and follow-up had to be a minimum of 6 months. Among the14 studies included in the analysis (N=230), mean follow-up was 14 months (range, 6 to 24). Outcomes of interest included response and remission rates at the last follow-up visit. Using raw scores, the response rate at last follow-up was 0.57 (95% CI, 0.44 to 0.69; p=.299; I^2=60.76%) and remission rate was 0.399 (95% CI,0.2923 to 0.5158; p=.09; I^2=42.80%).

Hitti et al (2020) conducted a meta-analysis and meta-regression of blinded studies that compared active deep brain stimulation to sham stimulation (12 trials, 186 patients).(54) Anatomic targets included the ventral anterior limb of the internal capsule, ventral capsule/ventral striatum, subcallosal cingulate, inferior thalamic peduncle, medial forebrain bundle, and lateral habenula. The most common target was the subcallosal cingulate. Meta-

analysis showed a modest reduction in depression rating scales (standardized mean difference =-0.75; 95% CI -1.13 to -0.36; p<.001) with moderate heterogeneity across studies (I2=59%). Meta-regression did not identify a significant difference between target areas. Adverse events included headache (26% of patients), visual disturbances (21%), worsening depression (16%), sleep disturbance (16%) and anxiety (14%).

Wu et al (2021) also conducted a meta-analysis of blinded studies that compared deep brain stimulation to control (placebo or sham stimulation). (76) There were 17 studies included, with a total of 233 patients, however, the majority were open-label studies (n=15). Anatomic targets included subcallosal cingulate gyrus (n=8), ventral capsule/ventral striatum (n=2), epidural prefrontal cortical (n=2), nucleus accumbens (n=1), superior lateral branch of the medial forebrain bundle(n=2), posterior gyrus rectus (n=1) and ventral anterior limb of the interna capsule (n=1). The pooled response rate estimate for the 2 RCTs was 1.45 (95% CI, 0.50 to 4.21) and for the open-label studies it was 0.56 (95% CI, 0.43 to 0.69); there was significant heterogeneity(I2 = 73.6%; p<.0001). The pooled estimate for remission rate in the open-label studies was 0.32 (95% CI, 0.25 to 0.39) with no statistical heterogeneity (I2 = 30.3%; p=.127); the pooled estimate for adverse events in the open-label studies was 0.67 (95% CI, 0.54 to 0.80) with significant heterogeneity (I2 =76.8%; p<.0001).

Controlled Trials

Ventral Capsule/Ventral Striatum
One of the studies included in the meta-analysis by Hitti et al was 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).(55) 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
Another study included in the meta-analysis by Hitti et al was a crossover RCT evaluating active and sham phases of DBS stimulation in 25 patients with treatment-resistant depression that was published after the systematic review.(56) 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 (≥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 limited sample size 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 Cingulate

Not included in the meta-analysis was a study by 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.(57) 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 1-month sham-controlled period and 11 patients had a 1-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 (≥ 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

Several prospective controlled trials and meta-analyses evaluating deep brain stimulation in patients with treatment resistant depression have been published. Six different target areas have been evaluated, most commonly the subcallosal cingulate. 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. 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

Review of Evidence

Systematic Review

Several systematic reviews evaluating DBS for obsessive-compulsive disorder (OCD) have been published.

Gadot et al (2022) published a systematic review of the efficacy of deep brain stimulation for treatment-resistant OCD and comorbid depressive symptoms.(71) Studies were included if they reported patient-level data on the effect of deep brain stimulation on the Yale-Brown Obsessive-Compulsive Scale. Thirty-four studies(N=352) were included in the analysis (9 RCTs, 25 nonrandomized trials) and both study types had a low risk of bias. Median follow-up in the included studies was 24 months (IQR, 12 to 32). Outcomes of interest included mean difference and percent reduction in the scale, and responder rate (defined as ≥35% reduction in Yale-Brown Obsessive-Compulsive Scale score). Random effects modeling found that Yale-Brown Obsessive-Compulsive Scale scores decreased by a mean of 47% (14.3 points; p<.01). The response rate at last follow-up was 66% (95% CI, 57% to 74%).

Mar-Barrutia et al (2021) evaluated both the short-term and long-term effects of deep brain stimulation for OCD, and included 29 studies (n=230) for short-term response and 11 studies (n=155) for long-term responses assessment; there were 7 total RCTs included. (77) Mean follow-up duration for the short-term and long-term studies was 1.5 years and 5.3 years, respectively. The authors noted that few studies were graded as low risk of bias, and there was marked heterogeneity among the studies reviewed which makes it difficult for comparison. The primary outcome measured was the Yale-Brown Obsessive-Compulsive Scale, and the mean changes in scores from pre- to post-treatment were similar in the short-term studies (change from 33.0 to 17.2) and the long-term studies (change from 34.4 to 18.0); however, significantly more patients met criteria for response in the long-term group (70.7%) versus the short-term group (60.6%). There were 26.6% of patients in the long-term group who were classified as non-responders.

A systematic review by Raviv et al (2020) identified 28 studies that met their criteria on deep brain stimulation for OCD, including 9 RCTs, 1 cohort study, 1 case-control study, 1 cross-sectional study, and 16 case series with more than 2 patients.(58) Only 4 studies were graded as low risk of bias, and the authors noted that there is no consensus on the optimal target. Striatal targets were the most common and included the anterior limb of the internal capsule, ventral striatum, nucleus accumbens, and caudate nucleus, but there was some discrepancy in nomenclature and overlap in stereotaxic coordinates. Additional targets included the subthalamic nucleus, bed nucleus of stria terminalis, inferior thalamic peduncle, and globus pallidus internus. The majority of studies utilized the Yale-Brown Obsessive Compulsive Scale; a score of 24 or more (of a possible 40) indicates severe illness. Responders were defined as at least 35% reduction in Yale-Brown Obsessive Compulsive Scale score and partial responders as a reduction between 25% and 35%. There was substantial variability in response for each target area, which may be related to the phenotypic diversity within the psychiatric diagnosis.

Kisely et al (2014) included only double-blind RCTs of active versus sham DBS.(59) Five trials (total n=50 patients) met eligibility criteria and data on 44 patients were available for meta-analysis. Three were parallel-group RCTs with or without a crossover phase and 2 were only crossover trials. The site of stimulation was the anterior limb of the internal capsule (3 studies), the nucleus accumbens (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). Most studies designated a therapeutic response as a reduction in Y-BOCS score of 35% or more from the pretreatment baseline, with a reduction of 25% to 35% considered a partial response. Only 1 of the 5 studies compared the proportion of responders on the Y-BOCS as an outcome measure and that study did not find a statistically significant difference between active and sham stimulation groups. When data from the 5 studies were pooled, there was a statistically significant reduction in the mean Y-BOCS in the active vs the sham group (MD = -8.49; 95% CI, -12.18 to -4.80). The outcome measure, however, does not permit conclusions on whether the between-group difference is clinically meaningful. Trial authors reported 16 serious adverse events including 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.

Section Summary: Obsessive-Compulsive Disorder
The literature on DBS for OCD includes RCTs and meta-analyses. Most studies had limited sample sizes and were at high risk of bias. Studies suggest that there may be improvements in OCD symptoms after deep brain stimulation treatment but have also identified a substantial number of adverse events and the optimal target(s) has not been determined. Additional blinded controlled studies are needed to draw conclusions about the impact of deep brain stimulation on the net health benefit.

OTHER NEUROLOGICAL AND PSYCHIATRIC DISORDERS

Review of Evidence

Multiple Sclerosis

Systematic Review
Brandmeir et al (2020) reported a meta-analysis of 13 studies of deep brain stimulation for multiple sclerosis tremor (129 patients received deep brain stimulation and 132 received medical management).(60) Results were compared for tremor severity after deep brain stimulation versus tremor severity at baseline and were combined across different target areas (ventral intermediate nucleus of the thalamus, ventral oralis nucleus of the thalamus, ventral caudal nucleus of the thalamus, zona incerta) and different levels of evidence. Four studies were rated as level II evidence, but the studies were not randomized and the sample size was limited, ranging from 4 to 12. Meta-analysis showed an improvement in the mean tremor score of 2.86 (95% CI 2.03 to 3.70, $p<0.001$). However, heterogeneity was high, suggesting that meta-analysis is not appropriate, and no distinction was made for the different anatomical targets. There was also evidence of publication bias.

Section Summary: Multiple Sclerosis
The literature on deep brain stimulation for multiple sclerosis tremor is characterized by a few non-randomized trials with a limited sample size and a variety of brain targets. Only one of the

controlled trials was conducted in the last decade. In addition to these limitations, there is evidence of publication bias. Literature does not currently support deep brain stimulation for multiple sclerosis tremor.

Chronic Pain

Systematic Review

Deer et al (2020) conducted a systematic review of deep brain stimulation for chronic pain.(61) They identified 1 RCT from 2017 with 10 patients with post-stroke pain syndrome and one RCT from 2010 with 11 patients who had chronic cluster headaches (described above). Three early case series (1990 to 2017, n=12 to 48) included patients with a variety pain conditions, including phantom limb pain, cancer, brachial plexus injury, failed back surgery, and spinal cord injury. The location of the stimulation was variable. Publication bias was not assessed.

Section Summary: Chronic Pain

Literature on deep brain stimulation for chronic pain is characterized by a few older studies (2 RCTs and 3 case series), published between 1990 and 2017, with a wide range of pain conditions and variety of targets. A systematic review of the evidence did not evaluate publication bias, which is suggested by the low number and age of publications.

Alcohol Use Disorder

Randomized Controlled Trial

Bach et al (2023) conducted a multicenter, double-blind, RCT of deep brain stimulation to the nucleus accumbens in 12 patients with treatment-resistant alcohol use disorder.(72) Deep brain stimulation was compared to sham stimulation over a 6 month period in hospitalized patients, followed by 12 months of unblinded treatment with deep brain stimulation in all patients. The primary outcome, continuous abstinence (ie, time to first alcohol use), was not significantly different between groups (p=.619), likely due to limited sample size/lack of power to find a difference. Secondary outcomes, including proportion of days abstinent (p=.048), alcohol craving as measured by the Alcohol Urge Questionnaire (p=.02), and anhedonia as measured by the Snaith-Hamilton Pleasure Scale (p=.028) were improved at 6 months with the deep brain stimulation group compared to sham stimulation. The authors stated that larger studies are needed to confirm these results.

Section Summary: Alcohol Use Disorder

A RCT in patients with alcohol use disorder did not find a difference in time to first alcohol use. Larger studies are needed to confirm the efficacy of deep brain stimulation in this population.

OTHER INDICATIONS

An exploratory study of the safety and tolerability of deep brain stimulation of the nucleus basalis of Meynert in 6 patients with dementia with Lewy bodies was reported by Gratwicke et al (2020).(62) Clinical outcomes were not evaluated. A pooled analysis by Shaffer et al (2023) of observational cohorts and case reports (n=36) of deep brain stimulation in patients with anorexia nervosa stated that there may be a benefit for deep brain stimulation to the subcallosal cingulate cortex in this population.(73)The evidence on use of DBS for anorexia nervosa, alcohol addiction, Alzheimer disease, and Huntington disease consists of 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 an 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 is superior to the other. The evidence is sufficient to determine that the technology results in an 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 an improvement in the net health outcome.

For individuals who have tardive dyskinesia or tardive dystonia who receive deep brain stimulation, the evidence includes a systematic review, an RCT and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The systematic review found an improvement in symptom severity with deep brain stimulation, but the authors noted some cases of symptom worsening or lack of improvement. All of the 14 included studies had small sample sizes (range, 2 to 22 patients). The RCT did not report statistically significant improvement in the dystonia severity outcomes or the secondary outcomes related to disability and quality of life, but these may have been underpowered. Additional studies, especially RCTs or other controlled studies, are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 first 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 7-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 second RCT (n=16) showed a benefit with DBS. Many 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 that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net 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 RCT, 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 that the technology results in an improvement in the net health outcome.

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 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 that the technology results in an improvement in the net health outcome.

For individuals who have obsessive-compulsive disorder who receive DBS, the evidence includes RCTs and meta-analyses. 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 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 that the technology results in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

For individuals who have other neurologic or psychiatric disorders who receive deep brain stimulation, the evidence includes a number of nonrandomized studies or RCTs in patients with multiple sclerosis, chronic pain, or alcohol use disorder. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One RCT with 10 multiple sclerosis patients, 2 RCTs in patients with chronic pain, and 1 RCT in patients with treatment-refractory alcohol use disorder is insufficient evidence on which to draw conclusions about the efficacy of deep brain stimulation in these populations. Additional trials are required. For individuals who have anorexia nervosa, Alzheimer disease, Huntington disease, or chronic pain who receive deep brain stimulation, the evidence includes case series; RCTs are needed to evaluate the efficacy of deep brain stimulation for these conditions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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), which were reaffirmed in 2022.(63) This update did not change the conclusions and recommendations of the AAN (2005) practice parameters on DBS for ET.(64) 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). This guideline is being updated.

Parkinson Disease

In 2018, the AAN affirmed the guideline developed by the Congress of Neurological Surgeons (Table 21).(65)

Tourette Syndrome

Guidelines from AAN (2019, reaffirmed 2022) provide recommendations on the assessment for and use of deep brain stimulation in adults with severe, treatment-refractory tics.(67) 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 anteromedialglobus pallidus is possibly more likely than sham stimulation to reduce tic severity.

American Society for Stereotactic and Functional Neurosurgery et al

Obsessive-Compulsive Disorder

In 2021, the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons updated their (2014) guidelines on DBS for obsessive-compulsive disorder.(68) 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 or bed nucleus of stria terminalis deep brain stimulation for medically refractory obsessive-compulsive disorder. It also concluded that the evidence on unilateral deep brain stimulation was insufficient.

Refractory Epilepsy

In 2022, the American Society for Stereotactic and Functional Neurosurgery published a position statement on deep brain stimulation for medication-refractory epilepsy.(74) Indications for deep brain stimulation include confirmed diagnosis of epilepsy (focal onset seizures with or without generalization), failure to achieve seizure control after 2 or more appropriately dosed seizure medications, seizures with localized onset in a region that cannot be resected or for which surgical resection has failed, or focal-onset seizures with a nonlocalized or unclear region of onset.

Congress of Neurologic Surgeons

Parkinson Disease

In 2018, evidence-based guidelines from the Congress of Neurologic Surgeons, affirmed by the AAN, 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.(65)

Table 21. 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 United Kingdom's National Institute for Health and Care Excellence (NICE) has published guidance documents on DBS, as discussed in the following subsections.

Tremor and Dystonia

In 2006, NICE made the same statements about the use of DBS for treatment of both tremor and dystonia.(69) 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 (70) 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 cephalalgias (eg, cluster headaches) was "limited and inconsistent, and the evidence on safety showed that there were serious but well-known adverse effects."(71)

Refractory Epilepsy

In 2020 , guidance from NICE indicated that the evidence on the efficacy and safety of deep brain stimulation for refractory epilepsy (for anterior thalamic targets) was limited in both quantity and quality, and "this procedure should only be used with special arrangements for

clinical governance, consent, and audit or research". (72) For targets other than the anterior thalamus, NICE recommends that "this procedure should only be used in the context of research".

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."(73) 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 22. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Epilepsy			
NCT04181229	Deep Brain Stimulation After Failed Vagal Nerve Stimulation for the Treatment of Drug-Resistant Epilepsy in Children	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			
NCT04244513[a]	Deep Brain Stimulation Treatment for Chorea in Huntington's Disease	40	Jun 2022
Obsessive-Compulsive Disorder			
NCT02773082[a]	Reclaim Deep Brain Stimulation Therapy for Obsessive-Compulsive Disorder (OCD)	50	Jan 2030
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 slMFB in Patients With Treatment Resistant Major Depression (FORSEEIII)	47	Jun 2023
Alzheimer Disease			
NCT03622905	ADvance II Study: DBS-f in Patients With Mild Alzheimer's Disease	210	Oct 2026
Unpublished			
NCT02076698	Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy	62	Nov 2021

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 intermedius 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

- Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy
- Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 27, 2023, 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	• 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	• 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		• Routine maintenance • Literature review r/t DBS for epilepsy
3/1/21	12/15/20		• Routine maintenance
3/1/22	12/14/21		• Routine maintenance
3/1/23	12/20/22		• Routine maintenance (ky)
3/1/24	12/19/23		• Routine maintenance • Vendor: N/A (ky)

Next Review Date: 4th Qtr, 2024

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.