Regence

Medical Policy Manual Surgery, Policy No. 84

Deep Brain Stimulation

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Next Review: March 2026
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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Deep brain stimulation (DBS) involves the stereotactic placement of electrodes into the brain (e.g., hypothalamus, thalamus, globus pallidus or subthalamic nucleus [STN]).

MEDICAL POLICY CRITERIA

Note: The use of spinal cord stimulation as a treatment of chronic pain is addressed in a separate policy (see Cross References section below).

I. When a multidisciplinary evaluation has confirmed both the medical intractability of the patient's symptoms and the potential value of deep brain stimulation (DBS), unilateral or bilateral DBS may be considered **medically necessary** when **both** of the following criteria (A. and B.) are met:

   A. One of the following is met:

      1. The request is for stimulation of the thalamus in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease. Disabling, medically unresponsive tremor defined as tremor causing significant limitation in daily activities AND inadequate symptom

control despite optimal medical management for at least three months before implant.

2. The request is for stimulation of the subthalamic nucleus or globus pallidus in patients with previously levodopa-responsive Parkinson's disease and symptoms such as rigidity, bradykinesia, dystonia or levodopa-induced dyskinesias.

3. The request is for stimulation of the subthalamic nucleus or globus pallidus in patients seven years of age or above with disabling, medically unresponsive primary dystonias including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis). Disabling, medically unresponsive dystonia defined as dystonia causing significant limitation in daily activities AND inadequate symptom control despite optimal medical management for at least three months before implant.

B. The patient does not have a medical condition that requires repeated MRI, OR if a medical condition requires **repeated MRI,** an **MR-conditional device** is used.

II. Unilateral or bilateral deep brain stimulation revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.

III. Deep brain stimulation is considered **not medically necessary** for essential tremor, Parkinson's disease, medically unresponsive primary dystonias including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis) when Criterion I. is not met.

IV. Deep brain stimulation is considered **investigational** for all other conditions (see Policy Guidelines).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Deep brain stimulation is considered investigational for indications that do not meet the policy criteria above including but not limited to the following:

- Cerebral Palsy
- Chronic pain (e.g., nociceptive pain; neuropathic pain)
- Cognitive decline/dementia due to Parkinson’s Disease
- Epilepsy/intractable seizures
- Huntington’s disease
- Multiple sclerosis
- Neuropsychiatric applications, including but not limited to the following:
    - Anorexia nervosa
    - Anxiety
    - Bipolar Disorder
    - Depression
    - Obsessive-compulsive disorder
    - Schizophrenia
    - Tourette syndrome
    - Alzheimer’s Disease

- Other movement disorders
- Post-traumatic tremor
- Tardive dyskinesia and tardive dystonia
- Traumatic brain injury (TBI)

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Multidisciplinary evaluations
- Indication for DBS
- Brain region to be stimulated
- Condition that is anticipated to require repeat MRI, if present.
- Name of DBS device

CROSS REFERENCES

1. Spinal Cord and Dorsal Root Ganglion Stimulation, Surgery, Policy No. 45
2. Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin, Surgery, Policy No. 205
3. Responsive Neurostimulation, Surgery, Policy No. 216

BACKGROUND

Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus or subthalamic nucleus [STN]). The electrode is initially attached to a temporary transcutaneous cable for short-term stimulation to validate treatment effectiveness. Several days later the patient returns to surgery for permanent subcutaneous implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. The electrode is typically implanted unilaterally on the side corresponding to the more severe symptoms. However, the use of bilateral stimulation using two electrode arrays is also used 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's disease, whose disease may progress over time, requiring different neurostimulation parameters. Setting the optimal neurostimulation parameters may involve the balance between optimal symptom control and appearance of side effects of neurostimulation, such as dysarthria, disequilibrium or involuntary movements.

DBS has been investigated for a variety of indications as discussed below:

- Alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy

  The technique has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of essential tremor, and tremor associated with Parkinson's disease (PD). More recently, there has been research interest in the use of deep brain stimulation of the globus pallidus or STN as a treatment of other Parkinsonian

symptoms such as rigidity, bradykinesia or 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., the "on" state) and the nadir response during drug troughs (i.e., the "off" state). In addition, levodopa, the most commonly used antiparkinson drug, may be associated with disabling drug-induced dyskinesias. Therefore, the optimal pharmacologic treatment of Parkinson's disease may involve a balance between optimal effects on Parkinson's symptoms vs. the appearance of drug induced dyskinesias. The effect of DBS on both Parkinson's symptoms and drug-induced dyskinesias has also been studied.

- Treatment of primary and secondary dystonia

  Dystonia is defined as a neurological movement disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, contorted, and painful movements or postures. In primary dystonia, dystonia is the only symptom and is unassociated with other pathology. Secondary dystonia is a dystonia brought on by an inciting event, such as a stroke, trauma, or drugs. Tardive dystonia is a form of drug-induced secondary dystonia. 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. Treatment options for dystonia include oral or injectable medications (i.e., botulinum toxin) and destructive surgical or neurosurgical interventions (i.e., thalamotomies or pallidotomies) when conservative therapies fail.

- Cluster headaches

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

- Other Neurologic/Psychiatric Conditions

  The role of DBS in treatment of other treatment-resistant neurologic and psychiatric disorders, particularly Tourette syndrome, epilepsy, obsessive-compulsive disorder (OCD), major depressive disorders, bipolar disorder, anorexia, alcohol addiction, and Alzheimer’s disease is also being investigated. Ablative procedures are irreversible and, though they have been refined, remain controversial treatments for intractable illness. Interest has shifted to neuromodulation through DBS of nodes or targets within neural

circuits involved in these disorders. Currently, a variety of target areas are being studied.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) has approved a number of deep brain stimulation systems for the treatment of essential tremor and tremor due to PD that is not adequately controlled by medication and is causing significant disability. The following DBS devices have been FDA-approved to treat essential tremor and PD-associated tremors under the Premarket Approval Application (PMA) process:

- Master Percept, Percept PC, And Activa® Deep Brain Stimulation Therapy Systems, with SenSight™ DBS accessories, Medtronic, Inc.
- Brio Neurostimulation System, Abbott St. Jude Medical Infinity™ Deep Brain Stimulation (DBS) system, Abbott (formerly St. Jude Medical).
- Vercise Deep Brain Stimulation System, including Vercise™ PC, Vercise Gevia™, and Vercise Genus™, Boston Scientific

The FDA has approved DBS systems for other indications. The Medtronic DBS System for Epilepsy (Medtronic, Inc) was FDA-approved through the PMA process as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Reclaim device (Medtronic, Inc.) was FDA-approved via the Humanitarian Device Exemption (HDE) process for the treatment of severe obsessive-compulsive disorder (OCD).

MR-conditional DBS devices may include the following devices. Please consult company websites for most up-to-date information.

- Medtronic: (*Medtronic DBS systems are MR Conditional and safe in the MR environment as long as certain conditions are met. If the conditions are not met, a significant risk is tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death.)
    - Activa™ RC system
    - Percept™PC neurostimulator
- Boston Scientific (*For the latest version of the safety manual, go to http://www.bostonscientific.com/manuals.)
    - Vercise Gevia™ DBS System

EVIDENCE SUMMARY

The principal outcome for deep brain stimulation (DBS) for any indication is symptom reduction and improved function. Assessment of the safety and efficacy of DBS requires well-designed and well-executed randomized controlled trials (RCTs) comparing DBS with sham or on- versus off- phases to determine the following:

- whether the benefits of DBS outweigh any risks
- whether DBS offers advantages over conventional treatments.

The evidence base is sufficient that deep brain stimulation (DBS) improves the net health outcomes of selected patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias. DBS has become a standard of care for these patients and may be considered medically necessary when criteria are met. Therefore, the evidence for DBS for these indications will not be reviewed in this policy. Below is a brief synopsis of the evidence for Parkinson's disease, essential tremor, or primary dystonias.

SYMTPOMS ASSOCIATED WITH PARKINSON'S DISEASE

Systematic Reviews and Technology Assessments

The policy for PD and tremor was initially based on two BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessments; a 1997 TEC Assessment focused on unilateral deep brain stimulation of the thalamus as a treatment for tremor[1] and a 2001 TEC Assessment focused on the use of deep brain stimulation of the globus pallidus and subthalamic nucleus for a broader range of Parkinson symptoms.[2]

A number of large systematic reviews have been published on the use of DBS for PD and tremor[3-13] confirming the efficacy of DBS in the control of motor signs and improvement of patients' functionality and quality of life.

Randomized Controlled Trials

There have been additional published RCTs of deep brain stimulation for PD, which continue to report overall positive results [14-23]. Some of these trials suggest that subthalamic stimulation was superior to medical therapy in patients with Parkinson's disease and early motor complications, while others did not find significant differences in overall health outcomes for patients. Surgery related adverse effects addressed in these RCTs indicate that the most common adverse effect is infection.

Nonrandomized Studies

Two new DBS systems with directional leads are currently available (approved by the Food and Drug Administration [FDA] in 2016 and 2017). Directional leads potentially enable clinicians to target more specific areas of the brain to be treated with the direct current. Published evidence consists of several small observational studies, with sample sizes ranging from 7 to 13.[24-27] The studies showed that patients experienced improved tremor scores and improved quality of life (QOL). Compared with historical data from conventional DBS systems, directional DBS widened the therapeutic window and achieved beneficial effects using lower current level. Comparative, larger studies are needed to support the conclusions from these small studies. Data from a large study of 292 patients are expected in 2018.

PRIMARY DYSTONIA

DBS for the treatment of primary dystonia received FDA approval through the Humanitarian Device Exemption (HDE) process.[28] The HDE approval process is available for those conditions that affect less than 4,000 Americans per year. According to this approval process, the manufacturer is not required to provide definitive evidence of efficacy, but only probable benefit. As noted in the FDA's analysis of risk and probable benefit, the only other treatment

options for chronic refractory primary dystonias are neurodestructive procedures. DBS provides a reversible alternative. The FDA summary of Safety and Probable Benefit states, “Although there are a number of serious adverse events experienced by patients treated with deep brain stimulation, in the absence of therapy, chronic intractable dystonia can be very disabling and in some cases, progress to a life-threatening stage or constitute a major fixed handicap. When the age of onset of dystonia occurs prior to the individual reaching their full adult size, the disease not only can affect normal psychological development but also cause irreparable damage to the skeletal system. As the body of the individual is contorted by the disease, the skeleton may be placed under constant severe stresses that may cause permanent disfigurement. Risks associated with DBS for dystonia appear to be similar to the risk associated with the performance of stereotactic surgery and the implantation of DBS systems for currently approved indications Parkinson’s Disease and Essential Tremor), except when used in either child or adolescent patient groups.”

The FDA HDE approval was based on the results of DBS in 201 patients represented in 34 manuscripts. There were three studies that reported at least ten cases. Clinical improvement ranged from 50 to 88%. A total of twenty-one pediatric patients were studied; 81% were older than seven years. Among these patients there was approximately a 60% improvement in clinical scores.

Since the FDA approval, there have been additional published randomized controlled trials of deep brain stimulation for dystonia, which continue to report positive results.[29-31] These trials included one with a long-term follow-up of five years. Two of the trials reported on the serious adverse effects of DBS, the majority of which were related to the implantation procedure. Dysarthria, involuntary movements and depression were common non-serious adverse events reported.[32]

In 2017, Moro published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia).[33] 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 two controlled studies, one RCT (described below) and one study that included a double-blind evaluation with and without stimulation. Twenty-four studies reported data using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and were included in a meta-analysis. These studies enrolled a total of 523 patients (mean per study, 22 patients) and had a mean follow-up of 32.3 months (range, 6 to 72 months). In a pooled analysis of BFMDRS motor scores (scale range, 0 to 120) from 24 studies, the mean increase in scores at six months compared with baseline was 23.8 points (95% CI 18.5 to 29.1 points). The mean increase in the motor score at last follow-up compared with baseline was 26.6 points (95% CI 22.4 to 30.9 points). The mean percentage improvement was 59% at six months and 65% at last follow-up. Fourteen studies reported BFMDRS disability scores (scale range, 0 to 30). Compared with baseline, the mean absolute change in the score was 4.8 points (95% CI 3.1 to 6.6 points) at six months and 6.4 points (95% CI 5.0 to 7.8 points) at last follow-up. The mean percentage improvement was 44% at six months and 59% at last follow-up. Rodrigues (2019) performed a Cochrane systematic review of RCTs and identified the same two RCTs.[32]

The remaining literature review below will focus on the use of DBS for the investigational indications in this policy.

TARDIVE DYSKINESIA AND TARDIVE DYSTONIA

Systematic Review

Grabel (2023) published a meta-analysis of clinical outcomes of DBS to treat tardive dystonia.[34] Fourteen studies were included that involved 134 patients. Studies were either single case reports or multiple case series. Using a random effects model on the summary mean data for each study yielded an estimated 70.56% overall mean improvement from DBS with high heterogeneity (I^2=93.91%). The authors acknowledge the possibility of positive selection bias due to the inclusion of single case studies. According to the authors no RCTs have been performed that evaluate DBS for TDD.

Tardive dyskinesia and dystonia (TDD) are severe side effects of dopamine-blocking agents, particularly antipsychotics. Little is known about the possible psychiatric complications of DBS in psychiatric patients. The mean improvement of TDD of the combined patients 3 to 76 months after implantation was 77.5% (95% CI 71.4% to 83.3%; p<0.000) on the Burke-Fahn-Marsden Dystonia Rating Scale.[35] The data suggest DBS could be effective and relatively safe for patients with treatment-resistant TDD; however, these results should be interpreted with caution, as most of the data are from case reports and small trials.

Mentzel (2015) performed a systematic review to assess the effects and side-effects of deep brain stimulation (DBS) in patients that have developed a severe debilitating treatment-resistant form of TDD.[36] This review included 19 case-reports and small-scale trials without randomization or blinding (n=52 patients). Using the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS), the Abnormal Involuntary Movement Scale (AIMS) and the Extrapyramidal Symptoms Rating Scale (ESRS), the investigators assessed the average improvement in the patients' condition, reporting that improvement as a result of DBS was statistically significant (p<0.00001) on all scales. However, limited conclusions can be drawn from this review on the efficacy and safety of DBS in this population, since there were no randomized controlled trials identified.

Randomized Controlled Trials

Stimulation of the globus pallidus has been examined as a treatment of tardive dyskinesia in a phase II double-blinded (presence and absence of stimulation) multicenter study.[37] The trial was stopped early due to successful treatment (greater than 40% improvement) in the first 10 patients.

Gruber (2018) assessed dystonia/dyskinesia severity using the Burke-Fahn- Marsden-Dystonia-Rating-Scale, BFMDRS at three months between active versus sham DBS.[38] 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 of the 25 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.

Nonrandomized Studies

Pouclet-Courtemanche (2016) reported on a case series of 19 patients with severe pharmaco-resistant tardive dyskinesia treated with DBS.[39] Patients were assessed after 3, 6, and 12 months after bilateral globus pallidus stimulation. At six 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%). An additional small (n=9) case series reported improvement in motor and disability scores.[40]

CEREBRAL PALSY

Koy (2022) published a prospective study aimed at assessing motor and nonmotor outcomes, with a focus on the quality of life (QOL) effects of DBS on pediatric patients with pharmacorefractory dyskinetic cerebral palsy. [41] The multi-site study enrolled 16 patients, age 8 to 18 years for the initial single-arm phase of the study, during which they were treated with DBS that targeted the globus pallidus internus for 12 months. After 12 months of DBS, 14 of the participants entered the second phase of the study; a randomized, double-blind crossover to either DBS for 24 hours followed by sham stimulation for 24 hours, or sham stimulation for 24 hours followed by DBS for 24 hours. The primary endpoint was mean change in the Caregiver Priorities & Child Health Index of Life and Disabilities (CPCHILD) questionnaire from baseline to 12 months. At 12 months the mean change in the CPCHILD score was not statistically significant (p=0.125). Of multiple secondary outcomes, significant results were improvement in Canadian Occupational Performance Measure performance scores from baseline to 12 months (change 1.1 +/- 1.2; [95% CI 0.2 – 1.9] points; p=0.02), and improvement in the Short-Form-36 physical health component noted by both patients and caregivers (patients, change 5.1 +/- 6.2 [95% CI 0.7 – 9.6] points; p= 0.028; caregivers, change 4.6 +/- 7.3 [95% CI 0.5 – 8.6] points; p=0.029). The authors state the statistically significant measures indicate improved performance of activities of daily living and physical health-related QOL for patients and caregivers. Seven other secondary outcome measures of physical health and QOL were not statistically significant. At randomization, there was no significant difference between stimulation modes (ON/OFF) in the BFMDRS-movement scores (p=0.141) or DIS (p=0.513). Limitations of the study include its small number of participants.

Koy (2013) reported data on the therapeutic outcomes of DBS in cerebral palsy.[42] Twenty articles comprising 68 patients with cerebral palsy undergoing deep brain stimulation assessed by the Burke-Fahn-Marsden Dystonia Rating Scale were identified. Most articles were case reports reflecting great variability in the score and duration of follow-up. The mean Burke-Fahn-Marsden Dystonia Rating Scale movement score was 64.94 ± 25.40 preoperatively and dropped to 50.5 ± 26.77 postoperatively, with a mean improvement of 23.6% ($p<0.001$) at a median follow-up of 12 months. The mean Burke-Fahn-Marsden Dystonia Rating Scale disability score was 18.54 ± 6.15 preoperatively and 16.83 ± 6.42 postoperatively, with a mean improvement of 9.2% ($p<0.001$). There was a significant negative correlation between severity of dystonia and clinical outcome ($p<0.05$). Authors suggest DBS can be an effective treatment option for dyskinetic cerebral palsy. In view of the heterogeneous data, a prospective study with a large cohort of patients in a standardized setting with a multidisciplinary approach would be helpful in further evaluating the role of deep brain stimulation in cerebral palsy.[43]

EPILEPSY/INTRACTABLE SEIZURES

DBS has been investigated for the treatment of intractable seizures in patients who do not respond to pharmacologic therapy. Approximately one-third of patients with epilepsy do not respond to anti-epileptic drugs and are considered to have drug-resistant epilepsy. Patients with drug-resistant or refractory epilepsy have a higher risk of death as well as a high burden of epilepsy-related disabilities and limitations. To date studies show promise but these early reports of therapeutic success are not confirmed by controlled clinical trials. Questions

regarding the best structures to stimulate, the most effective stimuli, and the contrasting effects of high-frequency and low-frequency stimulation remain unanswered.

Systematic Review

Haneef (2023) published a systematic review and meta-analysis comparing DBS to vagus nerve stimulation (VNS) and responsive neurostimulation (RNS) for generalized drug-resistant epilepsy.[44] Twenty studies, including eight using DBS were included. Mean follow-up time for DBS was 23.1 months and 39.1 months for VNS. RNS data were insufficient for analysis. Seizure reduction was greater for DBS (64.8%) than VNS (48.3%) (p=0.02). Studies addressing both treatments were deemed of moderate heterogeneity. Limitations include that only one DBS study was an RCT.

Skrehot (2023) also published a systematic review and meta-analysis comparing DBS to VNS and RNS for focal epilepsy.[45] The analysis included 24 studies, of which 11 were of DBS. This study also found that DBS was associated with greater seizure reduction than VNS (p<0.01) and that RNS and DBS had similar efficacy at one year follow-up. However, differences in efficacy narrowed by three-year follow-up to non-significant (p = 0.75).

Touma (2022) in collaboration with The International League Against Epilepsy (ILAE) Surgical Therapies Commission published a systematic review and meta-analysis to summarize the available evidence on DBS, vagus nerve stimulation (VNS), and responsive neurostimulation (RNS) in the treatment of drug-resistant epilepsy (DRE).[46] The analysis focused on the efficacy and tolerability of the three therapies for adults. The primary outcome measure was mean percentage decrease in seizure frequency. Thirty studies were included in the review. The majority were VNS studies. DBS was the intervention in only three studies. No study offered a head-to-head comparison of the treatments. Of the three studies involving DBS, one was an RCT, and the other two reported outcomes for the same cohort. The RCT found a significant difference in seizure frequency at 3 months between the intervention group and the control arm (p=0.0017), but the difference in seizure freedom was not statistically significant (relative risk [RR] = 0.3; 95% CI: 0.0, 8.2). Adverse events reported in the RCT include increased risk for depression (p=0.02) and memory impairment (p=0.03) in the intervention arm. However, long-term data showed mean seizure reduction of 69% at five years and 70% at seven years. There was also improvement in quality-of-life scores (QOLIE-31) at five years (p=0.001).

Rheims (2022) published a systematic review and meta-analysis of 28 studies investigating the impact of surgery and neuromodulation for drug-resistant epilepsy on mortality.[47] The authors note that the higher mortality rate in people with drug-resistant epilepsy is primarily due to epilepsy-related deaths. DBS procedure-related deaths specifically in people with drug-resistant epilepsy were not documented. The study cites an overall 0.2% postoperative in-hospital death rate from DBS for movement disorders. The rate of sudden unexpected death in epilepsy (SUDEP) was similar between DBS (2.9/1000 patient years [PY]) and RNS (2.8/1000 PY). The authors were unable to address whether DBS has a protective effect on SUDEP. When seizure freedom is established after surgery, the data suggest reduced mortality and decreased incidence of SUDEP. The available evidence on the potential impact of DBS on mortality from drug-resistant epilepsy is limited so definitive conclusions could not be drawn.

A 2022 systematic review by Vetkas evaluated the effectiveness of DBS of the anterior thalamic nucleus, the centromedian thalamic nucleus, and the hippocampus.[48] A total of 48 articles with 527 patients (sample sizes between 3 and 81) met inclusion criteria. For the

anterior thalamic nucleus, centromedian thalamic nucleus, and hippocampus there were two, two, and three RCTs (including the SANTE trial described below) and 23, 8, and 13 total studies, respectively. There was moderate to high heterogeneity (I^2 69 to 90%) for the anterior thalamic nucleus and the hippocampus and low heterogeneity for the centromedian thalamic nucleus. According to the meta-analysis, the mean seizure reduction after stimulation of the anterior thalamic nucleus, centromedian thalamic nucleus, and hippocampus was 60.8% (95% CI 55.72 to 65.89), 73.4% (95% CI 68.83 to 77.87), and 67.8% (58.14 to 77.46), respectively.

Two systematic reviews published in 2018 on the use of DBS for drug-resistant epilepsy assessed many of the same studies. The larger review, by Li (2018), identified 10 RCTs and 48 uncontrolled studies.[49] The literature search date was not reported. Meta-analyses were not performed. Summaries of the studies were discussed by area of the brain targeted by DBS. A review of the studies showed that DBS might be effective in reducing seizures when DBS targets the anterior nucleus of the thalamus or the hippocampus. Across studies, more than 70% of patients experienced a reduction in seizures by 50% or more. However, there were very few RCTs and the observational studies had small sample sizes. Individual responses varied, depending on seizure syndrome, presence or absence of structural abnormalities, and electrode position. Results were inconclusive when DBS targeted the centromedian nucleus of the thalamus, the cerebellum, and the subthalamic nuclei. Safety data on DBS was limited due to the small population sizes. The RCT in which DBS targeted the anterior nucleus of the thalamus (Fisher [2010] described below) reported paresthesias (23%), implant site pain (21%), and implant site infection (13%). Reviewers concluded that more robust clinical trials would be needed.

In a 2014 Cochrane review, updated in 2017, the safety, efficacy and tolerability of DBS and cortical stimulation were assessed in patients with refractory epilepsy.[50, 51] The reviews included RCTs comparing DPS to sham stimulation, resective surgery or further treatment with antiepileptic drugs. Of the 10 RCTs identified for inclusion in the 2014 review, three trials were specific to DBS (one anterior thalamic DBS trial, n=109 treatment periods; two centromedian thalamic DBS trials, n=20, 40 treatment periods). The studies added in the 2017 update were a cross-over RCT of bilateral anterior thalamic stimulation (n=4) and a double blind RCT of hippocampal stimulation (n=6) that was not included in the meta-analysis due to missing detailed methodology. The primary outcome measures included the proportion of patients who were disease free and a 50% or greater reduction in seizure frequency after one to three months. The evidence was rated as moderate quality and no statistical or clinically significant differences were reported based upon the primary outcome measures. Authors concluded that there is insufficient evidence upon which to draw conclusions regarding the efficacy and safety of hippocampal DBS or centromedian DBS as a treatment for epilepsy.

Randomized Controlled Trials

Fisher (2010) reported results of a multicenter, RCT of bilateral stimulation of the anterior nuclei of the thalamus for epilepsy (SANTE).[52] Fisher randomized patients who had failed at least three antiepileptic drugs to one of two groups, stimulation on or stimulation off. This was a 3-month double blind phase. After this phase, all patients received unblinded stimulation. During the first and second months of the blinded phase, the difference in seizure reduction between stimulation on and stimulation off was not significantly different (-42.1% vs. -28.7%, respectively). In the last month of the blinded phase, the stimulated group had a significantly greater reduction in seizures compared with the control group (-40.4% vs. -14.5%, respectively p=0.0017). During the blinded phase, the stimulation group experienced significantly fewer

seizure-related injuries than patients in the control group (7.4% vs. 25.5%, respectively p=0.01). Cognition and mood showed no group differences, but participants in the stimulated group were more likely to report depression (8 vs. 1, respectively) or memory problems (7 vs. 1, respectively) as adverse events. Depression symptoms resolved in four of the eight stimulated patients over an average of 76 days (range 14 to 145). There was a progressive reduction in seizure frequency over long-term follow-up. On intention-to-treat analysis, the median change in seizure frequency was -44% at 13 months and -57% at 25 months. By two years, 54% of patients had a seizure reduction of at least 50%, and 14 patients (13%) were seizure-free for at least six months. The most common device-related adverse events were paresthesias in 18.2% of participants, implant site pain in 10.9%, and implant site infection in 9.1%. Eighteen participants (16.4%) withdrew from the study after the implantation because of adverse events. There were five deaths, none of which were considered to be device-related. Although some patients appeared to have benefited from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the study, while significant, was modest.

Troster (2017) assessed neuropsychological adverse events from the SANTE trial during the three-month blinded phase, and at seven-year follow-up during the open-label noncomparative phase.[53] At baseline, there were no differences in depression history between groups. During the three-month blinded phase of the trial, depression was reported in eight (15%) patients from the stimulation group and in one (2%) patient from the no stimulation group (p=0.02). Memory adverse events also occurred at significantly different rates between the treatment groups during the blinded phase (seven in the active group, one in the control group; p=0.03). 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 and most cognitive function tests did not improve over baseline measurements.

A seven-year follow-up of SANTE was reported in the FDA SSED.[54] Seventy-three (66% of implanted) patients completed the year seven 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. 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.

Cukiert (2017) conducted a double-blind, placebo-controlled randomized trial evaluating outcomes of hippocampal stimulation in 16 patients with refractory temporal lobe epilepsy.[55] Prior to treatment, all patients had focal impaired awareness seizures (FIAS, complex partial seizures), and 87% had focal aware seizures (FAS, simple partial seizures). 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 nontreating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last 2 months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. There was a significant difference in FIAS frequency from the first month

of full stimulation until the end of the blinded phase (p<0.001) and FAS frequency for the same period except for the third month of the blinded phase.

Nonrandomized Studies

Peltola (2023) published long-term follow-up data on anterior nucleus of the thalamus (ANT) DBS therapy for 170 adults with drug resistant epilepsy from the Medtronic Registry for Epilepsy (MORE) registry.[56] MORE is an observational registry that collects prospective and retrospective data on adults with drug-resistant epilepsy being treated in 25 centers across 13 countries. After two years, the median monthly seizure frequency decreased by 33.1% (p<0.0001). A subgroup of 47 patients were followed for five years and had a 55% reduction in median seizure activity. Quality of Life in Epilepsy scores were improved by 2-points overall (p< 0.05), but data were available for only 78 people. Importantly, the most frequently observed adverse events were increased seizure frequency/severity in 16% of participants. Other adverse events were self-reported memory impairment (15%), self-reported depressive mood (15%). Limitations include reliability of self-reported data, non-protocolized visit windows, optional questionnaires and the use of retrospective data.

Kim (2017) conducted a retrospective chart review of 29 patients with refractory epilepsy treated with DBS.[57] Patients' mean age was 31 years, they had had epilepsy for a mean of 19 years, and had a mean preoperative frequency of tonic-clonic seizures of 27 per month. Mean follow-up was 6.3 years. Median seizure reduction from baseline was 71% at year one, 74% at year two and ranged from 62% to 80% through 11 years of follow-up. Complications included one symptomatic intracranial hemorrhage, one infection requiring removal and reimplantation, and two lead disconnections.

Long-term outcomes of the SANTE trial, described above, were reported by Salanova in 2015.[58] The uncontrolled open-label portion of the trial began after three months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician's discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the three-year follow-up, and 83 (75%) completed five years. Among patients with at least 70 days of diary entries, the median change in seizure frequency from baseline was 41% at one year and 69% at five years (p<0.001 for both). During the study, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first several months after implantation. The most frequently reported serious adverse events were implant site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the study and none were considered to be device-related. Depression was reported in 41 (37%) patients over the study; in three cases, this was considered device-related. Memory impairment (nonserious) was reported in 30 (27%) patients during the study, half of which had a history of the condition. Although some patients appear to have benefited from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the study, while significant, was overall modest.

TRAUMATIC BRAIN INJURY

Central thalamic deep brain stimulation (CT-DBS) has been investigated as a therapeutic option to improve behavioral functioning in patients with severe traumatic brain injury (TBI)[43]; however, there are no RCTs for this indication.

NEUROPSYCHIATRIC APPLICATIONS

In addition to the areas of research discussed above, DBS is being investigated for the treatment of Tourette syndrome, depression, addiction, alcohol addiction, anorexia, and obsessive compulsive disorder (OCD). Evidence remains insufficient to evaluate the efficacy of DBS for these disorders due to small sample sizes and other limitations in the available studies.[59]

Tourette Syndrome

Systematic Reviews

Zhang (2024) published a systematic review and meta-analysis of DBS for Tourette syndrome that includes 51 studies involving 673 people.[60] The study objective was to assess the efficacy of DBS for symptoms of Tourette's syndrome as well as associated co-morbidities. None of the included studies were RCTs. Using the Yale Global Tic Severity scale (YGTSS) the study found that the combined effectiveness of DBS showed significant improvement in tic severity (standardized mean difference [SMD] 1.88; 95% CI: 1.74 to 2.02, p <0.001). Subgroup analysis involving 23 studies found improvement in OCD symptoms (p <0.001), depression (p<0.001), and anxiety symptoms (p<0.001). The authors concluded that while the study findings are promising, the level of evidence in the included studies is low.

Wehmeyer (2021) conducted a pooled analysis of DBS for treatment-refractory Tourette syndrome.[61] A total of 65 studies with 376 patients were included. The primary outcome was Yale Global Tic Severity Scale (YGTSS) scores, which were significantly reduced at maximum follow-up of median 25 months (p<0.001). 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.

Baldermann conducted a systematic review that included 57 studies on DBS for Tourette syndrome, four of which were randomized crossover studies. The studies included a total of 156 cases.[62] Twenty-four studies included a single patient each and four had sample sizes of 10 or more (maximum, 18). Half of the patients (n=78) were stimulated in the thalamus and the next most common areas of stimulation were the global pallidus internus anteromedial part (n=44) and postventrolateral part (n=20). Two of the RCTs used thalamic stimulation, one used bilateral globus pallidus stimulation, and one used both. The primary outcome was YGTSS scores. In a pooled analysis of within subject pre-post data, there was a median improvement of 53% in the YGTSS, 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 the YGTSS and 54% and more than a 50% improvement. In addition, data were pooled from the four crossover RCTs; there were a total of 27 patients receiving DBS and 27 receiving 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). The authors noted that the effect size of 0.96 is considered to be a large effect.

A 2012 systematic review by Pansaon identified 25 published studies, representing data from 69 patients that reported on the efficacy of DBS in the treatment of Tourette syndrome.[63] However, only three studies with methodological quality ratings of fair to poor met the

inclusion criteria for evidence-based analysis. The authors recommend that DBS continues to be considered an experimental treatment for severe, medically refractory tics.

Randomized Controlled Trials

Kefalopoulou (2015) reported on double-blind crossover trial that included 15 patients with severe medically refractory Tourette syndrome.[64] They received surgery for bilateral globus pallidus internus DBS and were randomized to the off-position first or the on-position first for three months followed by the opposite position for the next three months. Fifteen patients underwent surgery 14 were randomized and 13 completed assessments after both on- and off-phases. For the 13 study completers, the mean YGTSS scores were 80.7 (SD=12.0) in the off-stimulation phase and 68.3 (SD=18.6) in the on-stimulation phase. Mean difference n YGTSS scores was 12.4 (95% CI 0.1 to 24.7) which was statistically significant (p=0.048) after Bonferroni correction. There was no between-group difference in YGTSS scores in patients who were randomized to the on-phase first or second. Three serious adverse events were reported, two related to surgery and one related to stimulation. The authors noted that the most effective target for DBS in Tourette syndrome patients needs additional study.

Piedad (2012) analyzed patient and target selection for DBS of Tourette syndrome. The majority of clinical trials for DBS in Tourette syndrome have targeted the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus.[65] Other targets that have been investigated include the subthalamic nucleus, caudate nucleus, globus pallidus internus, and the anterior limb of the internal capsule and nucleus accumbens. The review found no clear consensus in the literature for the best target or for which patients should be treated. Additional study is needed to clarify these issues.

In 2011, Ackermans reported preliminary results of a double-blind crossover trial of thalamic stimulation in six patients with refractory Tourette syndrome.[66] Tic severity during three months of stimulation was significantly lower than during the three months with the stimulator turned off, with a 37% improvement on the Yale Global Tic Severity Scale (mean 25.6 vs. 41.1) and a decrease in tic severity of 49% at one year after surgery compared to preoperative assessments (mean 21.5 vs. 42.2 – both respectively).Secondary outcomes (change in associated behavioral disorder and mood) were not altered by the stimulation. Serious adverse events included one small hemorrhage ventral to the tip of the electrode, one infection of the pulse generator, subjective gaze disturbances, and reduction of energy levels in all patients. The interim analysis led to the termination of the trial. The authors commented that further RCTs on other targets are urgently needed since the search for the optimal one is still ongoing.

Depression

The role of deep brain stimulation in treatment of other treatment-resistant depression, is also being investigated. Standard treatment modalities for treatment-resistant depression include psychotherapy, medication, and electroconvulsive therapy (ECT). However, even with a number of therapies being available, many patients can still remain symptomatic despite treatment. As an alternative therapy option, there have been multiple trials exploring deep brain stimulation in various cerebral targets for treatment-resistant depression.

Systematic Reviews

Reddy (2024) published a systematic review and meta-analysis to synthesize outcome data on DBS for treatment-resistant major depressive disorder.[67] The analysis included 15 studies, of which seven were RCTs. There were 275 participants in all 15 studies and 198 subjects in the seven RCTs. The analysis found that DBS led to an overall improvement of 47% in long-term depression scale scores during an average follow-up time of 21 months. However, when the analysis was limited to RCTs there was not a significant improvement compared to sham treatment. Open-label trials demonstrated a significantly greater improvement in depression scores than RCTs (55.9% vs. 35.3%; Q_M = 5.24, p=0.022). The authors noted the RCTs had larger sample sizes with stricter programming and reporting methods. The overall rate of serious adverse events from all 15 studies was 19% (n=53). The authors called for additional placebo-controlled studies to understand the effectiveness of DBS for treatment-resistant depression.

Sobstyl (2022) published a systematic review of studies that evaluated deep brain stimulation to the subcallosal cingulate cortex in patients with treatment resistant depression.[68] All study designs were considered but at least five patients were required and follow-up had to be a minimum of 6 months. Among the 14 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%).

Wu (2021) conducted a meta-analysis of blinded studies that compared deep brain stimulation to control (placebo or sham stimulation).[69] 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 two 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 (I^2 = 73.6%; p<0.0001). 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 (I^2 = 30.3%; p=0.127); the pooled estimate for adverse events in the open-label studies was 0.67 (95% CI 0.54 to 0.80) with significant heterogeneity (I^2 =76.8%; p<0.0001).

Hitti (2020) conducted a meta-analysis and meta-regression of blinded studies that compared active deep brain stimulation to sham stimulation (12 trials, 186 patients).[70] 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<0.001) with moderate heterogeneity across studies (I^2=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%).

In a recent systematic review, the literature was identified and reviewed for research findings related to treatment-resistant BD.[71] Therapeutic trials for treatment-resistant bipolar mania are uncommon and provide few promising leads other than the use of clozapine. Far more pressing challenges are the depressive-dysthymic-dysphoric-mixed phases of BD and long-

term prophylaxis. Therapeutic trials for treatment-resistant bipolar depression have assessed various pharmacotherapies, behavioral therapies, and more invasive therapies including electroconvulsive therapy (ECT), transcranial magnetic stimulation, and deep brain stimulation-all of which are promising but limited in effectiveness. Most studies identified in the review were small, involved supplementation of typically complex ongoing treatments, varied in controls, randomization, and blinding, usually involved brief follow-up, and lacked replication. Clearer criteria for defining and predicting treatment resistance in BD are needed, as well as improved trial design with better controls, assessment of specific clinical subgroups, and longer follow-up. Due to significant limitations within literature the effectiveness of DBS for bipolar treatment is not known at this time.

Controlled Trials

Crowell (2019) reported long-term follow-up of a within-subject trial with 28 participants with TRD or bi-polar II disorder who were treated with DBS of the subcallosal cingulate.[72] Patients were included who had depression for at least 12 months with non-response to at least three antidepressant medications, a psychotherapy trial, and electroconvulsive therapy (lifetime). Seventeen of the patients had a one-month sham-controlled period and 11 patients had a one-month open label period before the stimulation was turned on. Eight-year follow-up was available for 14 of the 28 participants. The primary outcome measure was the Illinois Density Index, which assesses the longitudinal area under the curve for behavioral measures; in this study these included response (>50% decrease from baseline) and remission (score <7) on the HAM-D. More than 50% of patients maintained a response and 30% in remission, over the eight years of follow-up. The physician-rated Clinical Global Impressions severity score improved from 6.1 (severely ill) at baseline to less than 3 (mildly ill or better) in this open label trial.

Obsessive-compulsive Disorder

The role of deep brain stimulation in treatment of OCD is also being investigated. This condition can be very debilitating and cause significantly reduced quality of life for patients. Conventional management strategies include cognitive-behavioral therapy, medications, and surgical intervention, however response to treatment may take months, and significant improvement with these therapies is not guaranteed. Deep brain stimulation may be an alternative therapy option for patients with treatment-refractory OCD, and some trials have explored safety and efficacy of this treatment for people with OCD.

Systematic Reviews

Gadot (2022) published a systematic review of the efficacy of deep brain stimulation for treatment-resistant OCD and comorbid depressive symptoms.[73] 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%).

Cruz (2022) conducted a systematic review and meta-analysis of 25 studies published between 2003 and 2020 that assessed the efficacy of DBS for severe and treatment-resistant OCD.[74] Severe OCD was defined as a score of between 24 and 31 on the Yale-Brown Obsessive Compulsive Scale (YBOCS). Treatment resistance was defined as resistance after at least 12 weeks of high-dose selective serotonin reuptake inhibitors (SSRI) therapy and augmentation strategies. Of the 25 studies analyzed, 8 were double-blinded clinical trials, all of which were included in the Raviv (2020) systematic review.[75] The analysis included 303 patients and mean follow-up was 36.98 months. Nearly 45% of the participants were female. Funnel plot was used to assess risk of bias. The meta-analysis found significant improvement in YBOCS scores after DBS (25 studies; SMD=2.39; 95% confidence interval [CI] 1.91-2.87; p<0.0001; $I^{2=}$72%). Analysis restricted to the eight RCTs also demonstrated significant improvement in YBOCS scores but heterogeneity was similar (8 studies; SMD=2.51; 95% CI, 1.80-3.22; p<0.0001; I^2=66%). Subgroup analysis found improved YBOCS scores after DBS with different targets, but could not assess all possible targets. Ventral capsule/ventral striatum (VC/VS) and nucleus accumbens (NAc) were the most frequently used targets (VC/BS, 5 studies; SMD=3.72; 95% CI, 1.25-6.18; p<0.0001; I^2=64%); Nucleus accumbens (NAc) (NAc, 3 studies; SMD=2.14; 95% CI, 1.46-2.81; P=0.003; I^2=89%). The analysis found DBS resulted in improvement in affective symptoms and functioning. Hamilton Depression Rating scores (HAM-D) significantly decreased, indicating clinical improvement (9 studies; SMD=1.19; 95% CI, 0.84-1.54; p<0.0001; I^2=17%). Hamilton Anxiety Rating scores (HAM-A) showed significant improvement (5 studies; SMD=1.00; 95% CI 0.32-1.69; p=0.004; I^2=59%). Global Assessment of Functioning scores also significantly improved after DBS (7 studies; SMD=-3.51; 95% CI, -5.00 - -2.02; p=0.005; I^2=90%). The study strengths include that it independently analyzed the four manifestations of OCD; YBOCS scores, and scores related to affective symptoms and functioning. Limitations include that there was high heterogeneity in most analyses and it was not possible to assess the effectiveness of all of the various DBS targets and modes of delivery. Safety of DBS was not addressed.

Mar-Barrutia (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.[76] 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 YBOCS 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 (2020) identified 28 studies that met their criteria on deep brain stimulation for OCD, including nine RCTs, one cohort study, one case-control study, one cross-sectional study, and 16 case series with more than two patients.[75] Only four 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.

Vicheva (2020) conducted a systematic review and meta-analysis of the use of DBS for treatment-resistant OCD.[77] Eight studies including 80 patients total met inclusion criteria. There was significant heterogeneity across studies. A meta-analysis of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores found a 38.68% pooled mean reduction. There were five severe surgery-related adverse events (intracerebral hemorrhage in three patients and infection in two patients) and eight severe mood-related serious adverse events (one completed suicide, three suicide attempts in two patients, and suicidal thoughts and depression in four). There were additional mild and transient adverse events.

Kisely conducted a systematic review and meta-analyses pooling study findings evaluating DBS for OCD, including only double-blind RCTs of active versus sham DBS.[78] Five trials (total N=50 patients) met eligibility criteria and data on 44 patients were available for meta-analysis. Three were parallel group RCTs with or without a crossover phase and two were only crossover trials. The site of stimulation was the anterior limb of the internal capsule (three studies), the nucleus accumbens (one study) and the subthalamic nucleus (one study). Duration of treatment ranged from 2 to 12 weeks. All studies reported scores on the Y-BOCS. This is a 10-item scale in which higher scores reflect more intense symptoms, and a score of 24 or more (of a possible 40) is considered severe illness. Most studies designate a therapeutic response as a Y-BOCS reduction of 35% or more from the pretreatment baseline, with a reduction of 25 to 35% or more considered a partial response. Only one of the five studies reported proportion of responders Y-BOCS as an outcome measure and that study did not find a statistically significant difference between active and sham stimulation groups. All studies reported the outcome measure, mean reduction in Y-BOCS. When data from the five studies were pooled, there was a statistically significantly greater reduction in the mean Y-BOCS in the active versus sham group (mean difference, -8.49; 95% CI 12.18 to -4.80). The outcome measure, however, does not allow conclusions on whether the difference between groups 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, five of increase in depressive or anxious symptoms and six of headaches.

Anorexia Nervosa

Anorexia nervosa is an eating disorder characterized by a chronic course that is refractory to treatment in many patients and has one of the highest mortality rates of any psychiatric disorder. Two systematic reviews and meta-analysis were published in 2022 to evaluate the efficacy of DBS in the treatment of anorexia nervosa. Neither review included RCTs. Karaszewska (2022) sought to estimate the overall effect of DBS in anorexia nervosa by evaluating the evidence of benefit in weight restoration, QOL, and reduction of psychiatric symptoms.[79] The primary outcome was body mass index (BMI) change after DBS. The secondary outcome was combined effect on psychiatric symptoms at the last observation. The meta-analysis included four studies with 56 participants. Only one participant was male. Follow-up periods ranged from 6 to 24 months. Random effects meta-analysis found improvement in BMI after DBS (Hedges's g=1.13; 95% CI=0.80-1.46; Z-value=6.75; p<0.001) without heterogeneity(I^2 =0.00, p=0.901). Meta-analysis also found improvement in combined

psychiatric symptom severity at last observation (Hedges's g=0.89; 95% CI=0.57-1.21; Z-value=5.47; p<0.001, I^2=4.29,p=0.371). The most common adverse effect (AE) was pain at the incision site. Less common reported AE's were cutaneous complications, hypomanic symptoms, auto-intoxication, and seizure. The risk of bias was deemed moderate for the primary study outcome of change in BMI, but serious for the secondary outcome measurements. The authors conclude that additional research on DBS therapy for anorexia nervosa is needed, but DBS may be considered an effective "last resort" treatment option for severe treatment-refractory anorexia nervosa.

The goals of the meta-analysis performed by Shaffer (2023) were to assess the efficacy of DBS on longitudinal BMI changes and compare DBS targets with anorexia nervosa.[80] The primary outcome measures were percentage BMI change at 6 and 9-12 months. Eleven studies with 36 participants were included, of whom 94.4% were female. Two of the studies were included in the Karaszewska (2022) review and five were single case studies. The overall mean percentage improvement in BMI was 12.63% at six months (SD 26.72%, n=34; 1.51 [3.28] kg/m^2) and 23.62% at 9-12 months (SD 32.62%, n=25; 2.62 [3.89] kg/m^2]. P-score rankings were calculated for DBS targets based on percentage BMI change at six and 9-12 months. The subcallosal cingulate cortex (SCC) (n=11) had the highest P-score at both time points (6-month: 0.9449, 9-12 month: 0.9771), and the ventral anterior limb of the internal capsule (VALC) (n=4) had the lowest (6-month: 0.0279, 9-12 month: 0.1179). Reported AEs that were considered most likely due to DBS included surgical site infection, pain or headache, seizure, skin ulceration, wound dehiscence or need for revision. Risk of bias in the six studies that included two or more subjects was determined to be small in five studies and fair in one. The authors concluded that there is insufficient evidence that supports DBS as clearly beneficial compared to standard therapy for anorexia nervosa.

In a systematic review by McClelland (2013), two case series and two case reports that applied DBS to anorexic patients were identified and reviewed with mixed results.[81] There are no RCTs investigating DBS for this indication.

Alcohol Addiction

Alcohol dependency can be considered as a chronic mental disorder characterized by frequent relapses even when treated with appropriate medical or psychotherapeutic interventions.

Bach (2023) published an RCT that compared DBS to sham stimulation in 12 male participants with at least a 10-year history of alcohol abuse disorder (AUD) that was treatment resistant.[82] All participants had DBS electrodes surgically placed and then were randomized to have either DBS or sham treatment for six months. Then the study was unblinded and all participants had 12 months of DBS therapy. Nine participants completed the study. The primary outcome measure was time to first alcohol use within six months after randomization. Secondary outcomes were alcohol consumption during the 18-month period after randomization, six subjective measures at 6 and 12 months after randomization, and safety outcomes. The difference between the groups in time to first alcohol use, the primary outcome measure, was not statistically significant (HR = 0.73; 95% CI 0.20-2.62; p=0.625). However, the participants randomized to DBS in the first six months had significantly more abstinent days at six months (p=0.048), a higher mean proportion of abstinent days (p=0.032), and fewer heavy drinking days (p=0.041). The DBS group also reported lower alcohol cravings after six months (p=0.020), but analysis across both groups showed lower

alcohol cravings at six months (p=0.014) compared to baseline. Both groups also had significantly higher proportion of abstinent days after 18 months (p=0.004). Further research with larger, more representative groups is needed to understand whether DBS is an effective therapy for alcohol addiction.

A 2012 systematic review by Herremans and Baeken investigated several neuromodulation techniques including deep brain stimulation in the treatment of alcohol addiction.[83] Previous studies investigating these neuromodulation techniques in alcohol addiction remain to date rather limited. Overall, the clinical effects on alcohol addiction were modest. Neuromodulation techniques have only recently been subject to investigation in alcohol addiction and methodological differences between the few studies restrict clear conclusions. Nevertheless, the scarce results encourage further investigation in alcohol addiction.

Alzheimer's Disease

A 2022 systematic review and meta-analysis by Cheyuo analyzed invasive and non-invasive neuromodulation therapies in the treatment of Alzheimer's Disease (AD).[84] Six studies were included in the meta-analysis, and of those, four involved DBS. The majority of the participants were in the two studies on non-invasive neuromodulation techniques. Of 242 total participants, 36 were from the four DBS studies. DBS was associated with improved cognitive outcome in people aged 65 years and older (p=0.004), but people younger than 65 years did not report better cognitive outcomes (p=0.65). Non-invasive neuromodulation techniques did not show improved cognitive outcome but were limited by lack of follow-up data. Further research is needed to understand the effect of DBS on cognitive function in people with AD.

OTHER APPLICATIONS

There is interest in applications of DBS beyond that for essential tremors, primary dystonia and Parkinson's disease. Clinical trials are being pursued; however, at this time, FDA approval is limited to the above indications and severe obsessive-compulsive disorder. The following discussion focuses on randomized controlled trials (RCTs) for the investigational indications noted in Policy Guidelines above.

Chronic Pain, Pain Syndromes, and Cluster Headaches

DBS for the treatment of chronic pain was investigated and largely abandoned in the 1980's due to poor results in two trials. With improved technology and surgical techniques there has been a resurgence of interest in DBS for intractable pain. DBS of the posterior hypothalamus for the treatment of chronic cluster headaches has also been investigated as functional studies have suggested cluster headaches have a central hypothalamic pathogenesis. Outcomes and treatment protocols have been heterogenous.

Qassim (2023) reported the results of an individual patient data meta-analysis investigating deep brain stimulation for chronic facial pain, including a total of 54 patients across seven studies.[85] The primary endpoint was the change in pain intensity using the visual analogue scale (VAS) at a defined time-point of 3 months or less after deep brain stimulation. Based on pooled data for 34 patients, the overall reduction in VAS at three months was 4.64 points (standard error, 0.54 points; p<.001). The authors noted that data for follow-up beyond 3 months were not eligible for statistical analysis and presented data from individual studies descriptively.

Mandat (2023) reported on seven patients with neuropathic facial pain who underwent deep brain stimulation of the periaqueductal and periventricular gray regions.[86] Efficacy was assessed using the Numeric Pain Rating Scale (NRS) and Neuropathic Pain Symptom Inventory (NPSI) before surgery and at three months, one year, and two years post-surgery. Four patients had pain from ischemic stroke, one from hemorrhagic stroke, and two from craniofacial injury. Results demonstrated that the NRS score decreased by 54% at three months, 48% at one year, and 45% at two years. The NPSI score decreased by 38% after three months, 32% after 12 months, and 34% after two years. The authors concluded that the effectiveness of therapy decreases at the two-year follow-up.

Membrilla (2023) published a systematic review (SR) and meta-analysis of interventions for preventative treatment of refractory chronic cluster headache.[87] Forty-five studies involving 106 participants were included. Of those, ten studies were on DBS, but only one was an RCT. The RCT was the same study included in the Deer (2020) SR described below. The other nine studies were observational and described a variety of DBS stimulation targets. The meta-analysis of the seven studies that reported response data found a pooled response rate of 77.0% (OR 0.770, 95% CI 0.594-0.947, I^2=78.9%, p<0.001). Adverse events included two deaths. One was directly due to the lead implantation procedure that led to cerebral hemorrhage. The authors note the studies showed high heterogeneity, and further research is needed on the safety and efficacy of DBS for chronic cluster headache.

Deer (2020) conducted a systematic review of deep brain stimulation for chronic pain.[88] They identified one 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.

Due to the limited RCTs and small sample sizes, conclusions cannot be reached on the effectiveness of DBS as a treatment of any type of pain, including but not limited to cluster headaches, chronic spinal pain, failed back surgery syndrome, phantom limb pain, facial deafferentation pain, and central or peripheral neuropathic pain.

Morbid Obesity

The study of DBS of the hypothalamus and nucleus accumbens for cluster headache and obsessive-compulsive disorder (OCD) has prompted interest in DBS for obesity and addiction, which are thought to be associated with those brain regions. However, patients with unilateral subthalamic nucleus or globus pallidus internus DBS for PD were found to have gained a mean 4.86 pounds following initiation of DBS.[89] Contreras (2022) performed a systematic review of the literature on DBS for the treatment of refractory obesity.[90] A total of seven studies including 12 patients met inclusion criteria. The incidence of moderate side effects was 33%. Statistical was not possible due to the limited amount of data available in the articles and the small study populations do not permit conclusions on efficacy of DBS for obesity.

Multiple Sclerosis

No randomized controlled trials were found for DBS in the treatment of multiple sclerosis (MS) tremors. Chagot (2023) reported on a retrospective study of 104 patients with MS tremor who underwent deep brain stimulation.[91] Three months after the intervention, data were available for 89 patients, of which 57 patients (64%) had clinical and functional improvement; 26 patients

had limited improvement and 6 patients had no improvement. Of the 57 patients who had clinical improvement at 3 months, 53 patients had sustained improvement at one year and 25 patients had sustained improvement at five years.

Brandmeir (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).[92] 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 number of subjects in these studies was small, 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. The small study populations do not permit conclusions on efficacy of DBS for MS tremors.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF NEUROLOGY

Guidelines from American Academy of Neurology (AAN) (2019, reaffirmed 2022) provide recommendations on the assessment for and use of deep brain stimulation in adults with severe, treatment-refractory tics.[93] AAN notes that patients with severe Tourette syndrome resistant to medical and behavioral therapy may benefit from DBS, 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 DBS of the anteromedial globus pallidus is possibly more likely than sham stimulation to reduce tic severity.

In the 2013 AAN guidelines on the treatment for tardive syndromes (TDS), indicated there is insufficient evidence to support or refute DBS for TDS.[94] This recommendation is based on Level U evidence (evidence is insufficient to support or refute the use of any other treatment over another). The 2011 AAN guideline regarding essential tremor was reaffirmed in 2014 indicating that, “no high quality, long-term studies exist regarding the efficacy and safety of (DBS) for ET.”[95]

The AAN updated its guidelines on the treatment of essential tremor (ET) in 2011.[95] This update did not change the conclusions and recommendations of AAN 2005 practice parameters on DBS for ET.[96] 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).

The 2010 guidelines from AAN on the treatment of nonmotor symptoms of PD found insufficient evidence for the treatment of urinary incontinence with DBS of the STN.[97] AAN found that DBS of the STN possibly improves sleep quality in patients with advanced PD.

However, none of the studies performed DBS to treat insomnia as a primary symptom, and DBS of the STN is not currently used to treat sleep disorders.

AMERICAN PSYCHIATRIC ASSOCIATION

In a 2007 the American Psychiatric Association (APA) published an evidence-based guideline, which was reaffirmed in 2012, on the treatment of patients with obsessive-compulsive disorder.[98] The APA gave their lowest level recommendation for DBS, among a list of other therapies with limited published evidence, for OCD that remains refractory "after first- and second-line treatment and well-supported augmentation strategies have been exhausted." In the 2010 APA guideline for the treatment of major depression, DBS is listed as a search term in the literature review; however, no recommendations for DBS are mentioned.[99]

CONGRESS OF NEUROLOGICAL SURGEONS AND AMERICAN SOCIETY FOR STEREOTACTIC AND FUNCTIONAL NEUROSURGERY

In 2020 the Congress of Neurological Surgeons (CNS) and the American Society for Stereotactic and Functional Neurosurgery updated the guidelines on DBS for obsessive-compulsive disorder, but the guideline is essentially unchanged since 2014:[100]

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

2018 evidence-based guidelines from the Congress of Neurological Surgeons (CNS) 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.[101]

Table 1. Recommendations of the Congress of Neurological 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

SUMMARY

There is enough research to show that deep brain stimulation (DBS) improves health outcomes in select patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias. DBS has become a standard of care for these patients. Therefore, DBS, including revision(s) or replacement(s), may be considered medically necessary when policy criteria are met.

Deep brain stimulation (DBS) is not clinically appropriate in patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias when criteria are not met. Therefore, DBS is considered not medically necessary for these indications when criteria are not met.

There is not enough research to determine the safety and effectiveness of deep brain stimulation (DBS) for other conditions. Therefore, DBS is considered investigational for all other indications when policy criteria are not met.

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CODES

Codes	Number	Description
CPT	61850	Twist or burr hole(s) for implantation of neurostimulator electrode(s), cortical
	61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
	61863	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
	61864	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure).

Codes	Number	Description
	61867	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
	61868	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	;with connection to two or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulsewidth, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95983	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
	95984	;with brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)
HCPCS	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
	L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension

Codes	Number	Description
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator

Date of Origin: *April 1998*