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Medical Policy Manual

Topic: Deep Brain Stimulation

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Section: Surgery

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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 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.

Deep brain stimulation (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 subthalamic nucleus (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, and alcohol addiction, 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 US Food and Drug Administration (FDA) has approved the Activa ® Tremor Control System(Medtronic Corp.) for deep brain stimulation.
The Activa® Tremor Control System and the Activa® Dystonia Therapy System consist of the following components:

1. The implantable pulse generator
2. The deep brain stimulator lead
3. An extension that connects the lead to the power source
4. A console programmer
5. A software cartridge to set electrical parameters for simulation
6. A patient control magnet, which allows the patient to turn the pulse generator on and off or change between high and low settings

In February 2009, the FDA approved deep brain stimulation with the Reclaim device (Medtronic, Inc.) via the Humanitarian Device Exemption (HDE) process for the treatment of severe obsessive-compulsive disorder (OCD).

Note: The use of spinal cord stimulation as a treatment of chronic pain is addressed in a separate policy, Surgery Policy No. 45, Spinal Cord Stimulation for Treatment of Pain.

MEDICAL POLICY CRITERIA

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** for:

   A. Stimulation of the thalamus in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease.

   B. Stimulation of the subthalamic nucleus (STN) or globus pallidus in patients with previously levodopa-responsive Parkinson's disease and symptoms such as rigidity, bradykinesia, dystonia or levodopa-induced dyskinesias.

   C. Stimulation of the STN or globus pallidus in patients 7 years of age or above with disabling, medically unresponsive primary dystonias including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis).

II. Disabling, medically unresponsive tremor or dystonia is defined as all of the following:

   A. Tremor or dystonia causing significant limitation in daily activities

   B. Inadequate symptom control despite optimal medical management for at least 3 months before implant

III. Contraindications to deep brain stimulation include:

A. Patients who are not good surgical risks because of comorbid medical problems or because of the presence of a cardiac pacemaker

B. Patients who have medical conditions that require repeated MRI

C. Patients who have dementia that may interfere with the ability to cooperate

IV. Deep brain stimulation is considered **investigational** for all other conditions, including, but not limited to the following:

A. Tardive dyskinesia and tardive dystonia

B. Cerebral Palsy

C. Traumatic brain injury (TBI)

D. Chronic pain (e.g., nociceptive pain; neuropathic pain)

E. Epilepsy/intractable seizures

F. Morbid obesity

G. Multiple sclerosis

H. Cognitive decline/dementia due to Parkinson's Disease

I. Other movement disorders

J. Post-traumatic tremor

K. Huntington's disease

L. Cluster headaches

M. Facial pain

N. Neuropsychiatric applications, including but not limited to the following:

1. Tourette syndrome

2. Depression

3. Bipolar Disorder

4. Obsessive-compulsive disorder

5. Schizophrenia

6. Anxiety

7. Anorexia nervosa

O. Treatment of addiction

- Alcohol addiction

SCIENTIFIC EVIDENCE[1]

Literature Appraisal

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 articles summarized below are representative of current clinical trial data.

Essential Tremor and Tremor in Parkinson's Disease (PD) and Tremor

Technology Assessments and Systematic Reviews

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[2] 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.[3] The following is a summary of the observations and conclusions of the TEC assessment:

- Unilateral deep brain stimulation of the thalamus for tremor[2]
    - 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 eight years, and side effects of stimulation were reported as mild and largely reversible. These results are 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.

- Unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus[3]
    - A wide variety of studies consistently demonstrated that DBS of the globus pallidus or subthalamic nucleus resulted in significant improvements as measured by standardized rating scales of neurologic function. The most frequently observed improvements consisted of increased waking hours spent in a state of mobility without dyskinesia, improved motor function during "off" periods when levodopa was not effective, reduction in frequency and severity of levodopa-induced dyskinesia during periods when levodopa was working ("on" periods), improvement in cardinal symptoms of Parkinson's disease during periods when medication was not working, and in the case of bilateral DBS of the subthalamic nucleus, 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 six to twelve months observed in most trials. While there was not a great deal of long-term follow-up, the available data were generally positive.
- Adverse effects and morbidity were similar to those known to occur with thalamic stimulation.
- Overall, the TEC Assessment concluded DBS poses advantages to other treatment options. In comparison to pallidotomy, DBS can be performed bilaterally. The procedure is non-ablative and reversible.

Articles published since these two Assessments continue to report positive outcomes for DBS for tremor and Parkinson's disease:

- A systematic review of 34 studies (921 patients) examined outcomes following subthalamic stimulation for patients with Parkinson's disease who had failed medical management (e.g., motor fluctuations, dyskinesia, and other medication side effects).[4] Twenty studies, primarily class IV (uncontrolled cohorts or case series), were included in the meta-analysis. Subthalamic stimulation was found to improve activities of daily living by 50% over baseline as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) part 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% improvement in the severity of motor symptoms while the patient was not taking medication. A strong relationship was found between the pre-operative dose response to L-dopa and improvements in both the UPDRS II and III. The analysis found a 56% reduction in medication use, a 69% reduction in dyskinesia, and a 35% improvement in quality of life with subthalamic stimulation.

- Appleby et al. reported on a meta-analysis focused on adverse events associated with DBS in order to assess the risks and benefits of the treatment as they relate to its potential use in the psychiatric setting.[5] They concluded that DBS was an effective treatment for PD, dystonia, and essential tremor, and rates of depression, cognitive impairment, mania, and behavior change were low. Prevalence of depression was 2–4%, mania 0.9–1.7%, emotional changes 0.1–0.2%, and suicidal ideation/suicide attempt was 0.3–0.7%. The completed suicide rate was 0.16–0.32%. In light of the rate of suicide in patients treated with DBS, particularly with thalamic and globus pallidus interna (GPi) stimulation, the authors argued for prescreening patients for suicide risk.

Systematic Review

- In a recent meta-analysis of RCTs, Perestelo-Pérez et al. described the efficacy of DBS in improving motor signs, functionality and quality of life of PD patients.[6] RCTs that compared DBS plus medication versus medication (alone or plus sham DBS) in PD patients were included. Outcome measures were motor function, waking time on good functioning without troublesome dyskinesias, levodopa-equivalent dose reduction, medication-induced complications, activities of daily living, health-related quality of life, and neurocognitive and psychiatric effects. Six RCTs (n = 1,184) that compared DBS plus medication versus medication alone were included. The results showed that DBS significantly improved patients' symptoms, functionality and quality of life. Effects sizes were intense for the reduction of motor signs and improvement of functionality in the off-medication phase, in addition to the reduction of the required medication dose and its associated complications. Moderate effects were observed in the case of motor signs and time in good functionality in the on-medication phase, in addition to the quality of life. Authors concluded that although the number of RCTs obtained was small, the total sample size was relatively large, confirming the efficacy of DBS in the control of motor signs and improvement

of patients' functionality and quality of life. More controlled research is required on the neurocognitive and psychiatric effects of DBS.

- A recent systematic literature review by Zappia and others identified pharmacologic and surgical therapy studies conducted on patients with ET and produced recommendations based on the analysis of evidence.[7] The literature was classified according to GRADE evidence profile, a system for grading the quality of evidence and the strength of recommendation based on the quality of the studies. The majority of studies included in the review were rated as "low" or "very low" for quality of evidence. Thalamic deep-brain stimulation was recommended for refractory ET. The results highlighted the need for well-designed direct comparison trials to define other possible treatment strategies for ameliorating the management of ET.

Randomized Controlled Trials

- In a recent study, 251 Parkinson's disease patients with early motor complications were randomly assigned to subthalamic stimulation plus medical therapy or medical therapy alone[8] in a 2-year trial. For the primary outcome of quality of life, the mean score for the neurostimulation group improved by 7.8 points, and that for the medical-therapy group worsened by 0.2 points. Neurostimulation was superior to medical therapy with respect to motor disability, activities of daily living, levodopa-induced motor complications, and time with good mobility and no dyskinesia. Authors suggest subthalamic stimulation was superior to medical therapy in patients with Parkinson's disease and early motor complications.
- The Netherlands sub thalamic and pallidal stimulation study (NSTAPS) assessed whether globus pallidus pars interna (GPi) deep brain stimulation (DBS) gives greater functional improvement than does subthalamic nucleus (STN) DBS.[9] The study enrolled 128 patients, assigning 65 to GPi DBS and 63 to STN DBS. Authors found no statistically significant difference in either primary outcome: mean change in weighted Academic Medical Center Linear Disability Scale (ALDS) in the GPi group compared to the STN group or the number of patients with cognitive, mood, and behavioural side-effects. Secondary outcomes showed larger improvements in off-drug phase in the STN group compared with the GPi group in the mean change in unified Parkinson's disease rating scale motor examination scores, the mean change in ALDS scores, and medication. Other secondary endpoints showed no difference between the groups. Although there was no difference in primary outcomes, the authors suggested that STN could be the preferred target for DBS in patients with advanced Parkinson's disease.
- The German Parkinson Study Group randomized 78 patient pairs with advanced Parkinson's disease and severe motor symptoms to either subthalamic stimulation or medical management.[10] Subthalamic stimulation improved severity of symptoms without medication in 55 of 78 pairs (from 48 to 28 on the UPDRS III). Improvements in quality of life were greater than medical management in 50 of 78 pairs (average change from 42 to 32 on the 100-point Parkinson's disease Questionnaire). Serious adverse events were more common with neurostimulation (13% vs. 4%) and included a fatal intracerebral hemorrhage. As part of this trial, Witt et al. performed an ancillary protocol to assess neuropsychiatric consequences of DBS in patients with Parkinson's disease.[11] One hundred-twenty-three patients with PD and motor fluctuations were randomized to DBS or best medical treatment. Neuropsychological and psychiatric examinations at baseline and 6 months post-implantation were compared. DBS of the subthalamic nucleus did not reduce overall cognition or affectivity. There was a selective decrease in frontal cognitive functions and an improvement in anxiety in patients after treatment that did not affect improvements in quality of life.
- Another European multicenter study assessed whether subthalamic stimulation might maintain quality of life and motor function if performed earlier in the course of the disease.[12] Ten

matched patient pairs younger than 55 years of age with mild to moderate motor signs were randomly assigned to DBS or medical management. However, in the medically treated patients both the daily dose of levodopa and the severity of levadopa-induced motor complications increased over the 18 months of the study (12% and 15%, respectively), while in the surgical patients the daily dose of levodopa was reduced by 57% and the severity of levodopa-induced motor complications improved by 83%. Additional studies are needed to determine the long-term effect of subthalamic stimulation in this younger patient population.

- In a randomized trial, Schuurman and colleagues followed 65 patients comparing thalamic stimulation and thalamotomy for treatment of tremor due to Parkinson's disease (PD) (45 patients), essential tremor (ET) (13 patients), and multiple sclerosis (MS) (10 patients).[13] After 5 years, 48 patients were available for follow-up: 32 with PD, 10 with ET, and 6 with MS. The primary outcome measure was functional status on the Frenchay Activities Index (FAI); secondary measures were tremor severity, frequency of complications, and patients' assessment of outcome. The mean difference in FAI scores was 4.4 (95% CI: 1.1–7.7) after 6 months, 3.3 (95% CI:-0.03–6.6) after 2 years and 4.0 (95% CI: 0.3–7.7) after 5 years in favor of stimulation. Tremor suppression was equally effective after both procedures, and stable in PD patients. A diminished effect was observed in half of the patients with ET and MS. Small numbers of patients with ET and MS limit conclusions with respect to these conditions. Neurological adverse effects were higher after thalamotomy. Subjective assessments favored stimulation. Hariz et al. evaluated outcomes of thalamic DBS in patients with tremor predominant PD who participated in a multicenter European study and reported that, at 6 years post-surgery, tremor was still effectively controlled and appendicular rigidity and akinesia remained stable when compared with baseline.[14]
- Weaver and colleagues report 6-month outcomes of a multicenter randomized, controlled trial comparing DBS with best medical therapy for patients with advanced PD.[15] Of 278 patients that were screened, 255 were randomized; 134 to best medical therapy and 121 to DBS (61 to stimulation of the globus pallidus and 60 to stimulation of the subthalamic nucleus). By intention-to-treat analysis, patients who received DBS gained a mean of 4.6 hours/day of on time without troubling dyskinesia compared to no hours gained for patients receiving best medical therapy ($p<0.001$). Seventy-one percent of DBS patients experienced clinically meaningful motor function improvements (i.e., >5 point change in Unified Parkinson Disease Rating Scale of motor function) versus 32% of best medical therapy group. Significantly greater improvements in quality of life measures were achieved by DBS patients. At least one serious adverse event occurred in 49 DBS patients versus 15 in the best medical therapy patients, including 39 related to the surgical procedure and one death secondary to cerebral hemorrhage.

- Williams et al. reported results from an ongoing randomized, multicenter open-label trial (PD SURG) from 13 neurosurgical centers in the United Kingdom.[16] Included in the study were 366 patients with PD that was not adequately controlled by medical therapy. Patients were randomized to surgery DBS and best medical therapy, or to best medical therapy alone. The study was designed to detect a 10-point difference (regarded as clinically important) in the Parkinson's disease questionnaire (PDQ) summary index. Five of 183 patients randomized to surgery did not have surgery, and 12 of 183 patients randomized to medical therapy had surgery within the first year of the study (patients were analyzed in the treatment group to which they were randomized). In 174 patients, the subthalamic nucleus was the surgical target, and 176 of 178 procedures were bilateral. At 1 year, the mean improvement in the primary outcome measure, the PDQ summary index, was 5.0 points in the DBS group and 0.3 points in the control group. The difference in mean change in PDQ between the 2 groups was -8.9 for the mobility domain, -12.4 for the daily living domain, and -7.5 for the bodily discomfort domain.

Differences between groups in the other domains were not significant. Thirty-six (19%) patients had serious surgery-related adverse events including one procedure-related death. The most common surgery-related serious adverse events were infection (n=16).

Primary Dystonia

DBS for the treatment of primary dystonia received FDA approval through the Humanitarian Device Exemption (HDE) process.[17] 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."

Meta-analyses

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 trials of deep brain stimulation for dystonia, which continue to report positive results.

Randomized Controlled Trials

The Deep-Brain Stimulation for Dystonia Study Group compared bilateral pallidal neurostimulation with sham stimulation in 40 patients with dystonia who had failed medical management (3-month randomized trial with a 6-month open-label extension).[18] Blinded assessment with the Burke-Fahn-Marsden Dystonia Rating Scale found improvements in the movement score (16 points vs. 1.6 points in sham controls), which corresponded to a 39% reduction in symptoms. Disability scores improved by 4 points in the neurostimulation group compared with a 0.8-point improvement in the control subjects (38% improvement). The study found a 30% improvement in quality of life (change of 10 vs. 4 points in controls) following stimulation of the globus pallidus. There was high variability in baseline scores and in the magnitude of improvement; 6 patients (17%) were considered to have failed treatment (< 25% improvement), 5 patients (25%) improved by more than 75%. No single factor was found to predict the response to treatment. Independent assessors found similar improvements in the control group after the 6-month open-label extension. In a follow-up study, 38 patients (95%) agreed to be followed up annually, and 80% of patients completed 5-year follow-up.[19] Intention-to-treat analysis showed significant improvements in dystonia severity at 6 months (-47.9%), 3 years (-61.1%), and 5 years (-

57.8% compared with baseline). The unmasked raters tended to score dystonia severity as higher than the 2 masked raters in the original study. Responder analysis (> 25% on the BFMDRS) indicated a positive response in 83% of 36 patients at 6 months, 94% of 31 patients at 3 years, and 81% of 32 patients at 5 years. There were 21 serious adverse events that required hospitalization. Almost all serious adverse events were device related including subcutaneous infection, lead dislodgement/lead breakage, and stimulator malfunction. The most common non-serious adverse event was dysarthria.

Tardive dyskinesia and tardive dystonia

Systematic Review

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%-83.3%; P < .000) on the Burke-Fahn-Marsden Dystonia Rating Scale.[20] 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.

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.[21] The trial was stopped early due to successful treatment (greater than 40% improvement) in the first 10 patients.

No comparative trials were found for DBS for tardive dystonia, though one small (n=9) case series reported improvement in motor and disability scores.[22]

Cerebral Palsy

Koy and others recently reported data on the therapeutic outcomes of DBS in cerebral palsy.[23] 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 < .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 < .001). There was a significant negative correlation between severity of dystonia and clinical outcome (P < .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.[24]

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 IV.A-O 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. However, due to the lack of RCTs, 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.

Epilepsy/Intractable Seizures

DBS has been investigated for the treatment of intractable seizures in patients who are not surgical candidates. 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.

One multicenter, RCT of bilateral stimulation of the anterior nuclei of the thalamus for epilepsy (SANTE) was found in the published literature.[25] Fisher et al randomized patients who had failed at least 3 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 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 4 of the 8 stimulated patients over an average of 76 days (range 14-145). 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 2 years, 54% of patients had a seizure reduction of at least 50%, and 14 patients (13%) were seizure-free for at least 6 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 5 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 was modest. Additional study is needed to establish the safety and efficacy of this treatment.

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.[26] There are currently no studies of DBS in any brain region for the treatment of obesity.

Multiple Sclerosis

No randomized controlled trials were found for DBS in the treatment of multiple sclerosis (MS) tremors. Three small nonrandomized comparative trials were found, one[27] comparing stimulation off versus on (n=9), and 2[13,28] comparing thalamic stimulation versus thalamotomy (n=12 total MS patients). The small study populations do not permit conclusions on efficacy of DBS for MS tremors.

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Traumatic brain injury (TBI)

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)[24]; 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.[29] Evidence remains insufficient to evaluate the efficacy of DBS for these disorders.

- Tourette Syndrome

  A 2012 systematic review identified 25 published studies, representing data from 69 patients that reported on the efficacy of DBS in the treatment of Tourette syndrome.[30] However, only 3 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.

In an additional systematic review from 2012, authors 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.[31] 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 et al. reported preliminary results of a double-blind crossover trial of thalamic stimulation in 6 patients with refractory Tourette syndrome.[32] Tic severity during 3 months of stimulation was significantly lower than during the 3 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 1 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.

- Major Depression

  A variety of target areas are being investigated in case series for DBS of treatment-resistant depression, including the subcallosal cingulate gyrus, the ventral capsule/ventral striatum, and the nucleus accumbens. No randomized controlled trials have been identified.

- Bipolar disorder (BD)

  Many patients diagnosed with bipolar disorder (BD) respond incompletely or unsatisfactorily to available treatments. Therapeutic trials for treatment-resistant bipolar mania are uncommon, and provide few promising leads other than the use of clozapine.

  In a recent systematic review, the literature was identified and reviewed for research findings related to treatment-resistant BD.[33] 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.

- Obsessive-compulsive disorder

  In 2011, de Koning et al. published a systematic review of clinical trials for DBS for treatment resistant obsessive-compulsive disorder (OCD).[34] Nine case studies and 7 controlled studies with a blinded on-off phase were included. Inclusion criteria were use of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) as an outcome measure, and "some estimate of efficacy" included in the study report. The authors concluded that DBS may be a beneficial and safe therapy for refractory OCD, but further research is needed to establish appropriate patient selection criteria, determine the more effective target location, and optimize post-operative patient management. Of note, the systematic review discussed the reported outcomes of the selected studies, but failed to critically appraise their quality.

  Of the studies included in the systematic review:

  - Nine case studies consisted of observational case reports of 1-2 patients, or small (<10 patients) non-comparative case series. Conclusions cannot be reached from these studies as randomized trials with an appropriate comparison group are needed to control for any placebo effect and for potential patient selection and treatment bias. In addition, the lack of blinding of patients and investigators fails to control for the placebo effect and potentially leads to additional bias.
  - All seven RCTs included in the systematic review were double-blind crossover studies in which both the patient and the investigators were blinded to whether the DBS was turned on or off.[35-41] However, these RCTs are considered unreliable for the following reasons:

    - Small study populations (n= 4 to 16) limit the ability to rule out the role of chance as an explanation of findings
    - Heterogeneity of study participants (e.g., comorbidities) and procedures (e.g., five different brain target areas) limits meaningful comparison of outcomes
    - Inability to isolate the contribution of DBS from the impact of other treatments (e.g., medications) during the study period
    - Short-term follow-up does not permit conclusions related to the durability of any initial beneficial effects

  No new randomized controlled trials have been published since this 2011 systematic review.

- 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. In a recent systematic review by McClelland et al., 2 case series and 2 case reports that applied DBS to anorexic patients were identified and reviewed with mixed results.[42] 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.

A 2012 systematic review by Herremans and Baeken investigated several neuromodulation techniques including deep brain stimulation in the treatment of alcohol addiction.[43] 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.

Clinical Practice Guidelines and Position Statements

American Academy of Neurology (AAN)

In the 2013 AAN guidelines on the treatment for tardive syndromes (TDS), the report states there is insufficient evidence to support or refute DBS for TDS.[44] This recommendation is based on Level U evidence (evidence is insufficient to support or refute the use of any other treatment over another). In the 2011 guidelines, the AAN states that DBS of the ventral intermediate nucleus thalamic nucleus effectively reduces limb tremor and is recommended for treatment of medically refractory essential tremor of the limbs.[45]

American Psychiatric Association (APA)

In a 2007 evidence-based guideline on treatment of patients with obsessive-compulsive disorder, 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."[46] 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.[47]

Veterans Health Administration, Department of Defense (VA/DoD)

A 2010 evidence-based update of the VA/DoD practice guideline for the management of post-traumatic stress stated that the evidence is insufficient to recommend the use of biomedical somatic therapies including deep brain stimulation for first-line treatment of post-traumatic stress disorder.[48]

Summary

- There is evidence from multiple randomized controlled trials that 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 therefore be considered medically necessary.
- There is insufficient evidence to determine the safety and efficacy of DBS for conditions other than Parkinson's disease, essential tremor, or primary dystonias. Therefore, it is considered investigational for all other indications.

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CROSS REFERENCES

Spinal Cord Stimulation for Treatment of Pain, Surgery, Policy No. 45

CODE	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

CODE	NUMBER	DESCRIPTION
	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).
	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
	95970	Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (i.e., cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming
	95978	Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode select ability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming, first hour
	95979	Complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming, each additional 30 minutes after first hour
HCPCS	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each

CODE	NUMBER	DESCRIPTION
	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
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator