Cigna Medical Coverage Policy

Subject  Deep Brain, Motor Cortex and Responsive Cortical Stimulation

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Coverage Policy

Deep Brain Stimulation
Cigna covers deep brain stimulation (DBS) as medically necessary for the treatment of ANY of the following:

- chronic, medically intractable primary dystonia (including generalized and/or segmental dystonia, hemidystonia, or cervical dystonia/torticollis) for an individual seven years of age or older when used in accordance with the Humanitarian Device Exemption (HDE) specifications of the U.S. Food and Drug Administration (FDA)
- chronic, medically intractable Parkinson disease (PD) when an individual meets ALL of the following criteria:
  - has intractable motor fluctuations, dyskinesia or tremor
  - is levodopa-responsive
  - does not have a significant mental impairment (e.g., dementia, severe depression) or a medical (e.g., stroke, cardiovascular disease) or surgical (e.g., previous ablative surgery such as thalamotomy, pallidotomy) contraindication to DBS
- chronic, medically intractable essential tremor (ET)

Cigna covers the replacement/revision of a deep brain stimulator generator/battery and/or lead/electrode and/or patient programmer as medically necessary for an individual who meets ALL of the above criteria and the existing generator/lead/programmer is no longer under warranty and cannot be repaired.
Cigna does not cover DBS for any other indication including, but not limited to, obsessive-compulsive disorder because it is considered experimental, investigational or unproven.

**Responsive Cortical Stimulation**

Cigna covers responsive cortical stimulation (e.g., NeuroPace® RNS® System) as medically necessary when ALL of the following criteria are met:

- age 18 years or older
- partial onset seizures
- seizures are refractory to two or more antiepileptic medications
- experiencing an average of three or more disabling seizures (e.g., motor partial seizures, complex partial and/or secondarily generalized seizures) per month over the three most recent months
- diagnostic testing confirms localized seizure onset to one or two foci
- not a candidate for focal resection epilepsy surgery
- not a candidate for vagus nerve stimulation

Cigna covers the replacement/revision of a responsive cortical stimulation neurostimulator/battery and/or leads and/or monitor as medically necessary for an individual who meets ALL of the above criteria and the existing neurostimulator/lead/monitor is no longer under warranty and cannot be repaired.

**Motor Cortex Stimulation**

Cigna does not cover motor cortex stimulation for any indication because it is considered experimental, investigational or unproven.

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**General Background**

**Deep Brain Stimulation**

Deep brain stimulation (DBS) involves the delivery of continuous, high-frequency electrical impulses to an area in the brain responsible for movement. The procedure is reversible and causes no permanent damage. Prior to implantation, a stereotactic rigid frame, or frame based system, is secured to the patient's skull, and the initial targeted area is selected using an imaging technique (e.g., magnetic resonance imaging [MRI], computed tomography [CT] or ventriculography). An alternative to the frame-based system is the frameless stereotactic system which may use external fiducial markers and/or internal anatomic landmarks. An electrode is introduced into the brain and test simulations are performed to evaluate and adjust tremor amplitude, diffusion of stimulation and determination of the threshold for paresthesias and speech disturbances. The electrode is connected to a computerized pulse generator which is typically implanted underneath the skin near the collarbone. The DBS system may be implanted either unilaterally or bilaterally, depending on the distribution of the patient’s symptoms. When the intended targets include both sides of the brain, two separate systems are implanted. The system also includes a handheld therapy controller and a control magnet. Batteries in the generators typically last from three to five years and are replaced in an outpatient procedure. Some newer devices may have a rechargeable battery (Medtronic, 2015; Weintraub, et al., 2007; Holloway, et al., 2005).

DBS is used for a carefully selected subset of individuals with chronic primary dystonia including generalized and/or segmental dystonia, cervical dystonias (i.e., torticollis), and hemidystonia. In addition, DBS is considered an established intervention for the treatment of medically refractory essential tremor (ET) and Parkinson disease (PD). DBS is not a first line therapy and is generally considered when the individual cannot tolerate or has failed pharmacotherapy or when pharmacotherapy is no longer effective.

**U.S. Food and Drug Administration (FDA)**

The Activa® Dystonia Therapy System (Medtronic Neurological, Minneapolis, MN) was FDA-approved under the Humanitarian Device Exemption (HDE) process. The device was approved for “unilateral or bilateral stimulation of the internal globus pallidus (GPI) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (i.e., drug-refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (i.e., torticollis) in patients seven years of age or above” (FDA, 2003).
The Activa® Tremor Control System (Medtronic) was approved by the FDA under the premarket approval process (PMA) for “unilateral thalamic stimulation for the suppression of tremor in the upper extremity in patients who are diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability” (FDA, 1997).

The Activa® Parkinson’s Control Therapy System (Medtronic) is FDA approved as a PMA device for “bilateral stimulation of the internal globus pallidus (GPI) or the subthalamic nucleus (STN) for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson’s disease that are not adequately controlled with medication” (FDA, 2002). June 2015 the Brio Neurostimulation System (St. Jude Medical, Plano, TX) is FDA approved as a PMA device for the following indications: 1) bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinson’s disease that are not adequately controlled by medications; 2) unilateral or bilateral stimulation of the ventral intermediate nucleus (VIM) of the thalamus for the suppression of disabling upper extremity tremor in adult essential tremor patients whose tremor is not adequately controlled by medications and where the tremor constitutes a significant functional disability. The Brio is a rechargeable system.

In February 2009, the Medtronic Reclaim™ DBS™ Therapy for OCD system was FDA approved as a HDE device and is “indicated for bilateral stimulation of the anterior limb of the internal capsule (AIC) as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant obsessive-compulsive disorder (OCD) in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs)”.

The HDE labeling for the Reclaim system stated that “The safety and probable benefit of DBS for the treatment of OCD has not been established for the following:

- patients with Tourette’s syndrome
- patients with primary subclassification of hoarding
- patients whose OCD is documented to be less than five years duration
- patients whose Yale-Brown Obsessive-Compulsive Scale (YBOCS) score is less than 30
- patients who have not completed a minimum of three adequate trials of first and/or second line medications with augmentation
- patients who have not attempted to complete an adequate trial of cognitive behavior therapy (CBT)
- patients with a previous surgical ablation procedure (e.g., capsulotomy)
- patients who are pregnant
- patients who are under the age of 18 years
- patients with dementia
- patients with coagulopathies or who are on anticoagulant therapy
- patients without comorbid depression and anxiety
- patients with neurological disorders
- patients with other serious medical illness including cardiovascular disease, renal or hepatic failure, and diabetes mellitus”

The labeling also stated that “Physicians should carefully consider the potential risks of implanting the brain stimulation system in patients with comorbid psychiatric disorders, including:

- bipolar disorder
- body dysmorphic disorder
- expanded personality impulse-control disorders or paraphilias
- psychotic disorder
- severe personality disorders
- substance abuse
- the inability to control suicidal impulses or a history of suicide attempts

The brain stimulation system may aggravate the symptoms of comorbid psychiatric disorders” (FDA, 2009).

Dystonia
Dystonia refers to a diverse group of movement disorders characterized by involuntary muscle contractions that may cause twisting and repetitive movements or abnormal postures. Primary dystonia often begins focally in the legs and progresses to a generalized (i.e., involving all of the body) syndrome. Secondary dystonias are induced by a disease or ingested substance. Dystonias may also be categorized as focal (i.e., one area of the body is involved, such as hemidystonia, cervical dystonia or torticollis), or segmental involving two or more areas.

Treatment options for dystonia include oral medications and chemodenervation (e.g., botulinum toxin [BTX], type A or type B injection therapy). Invasive interventions and surgery for dystonia are generally reserved for those patients who have significant disabilities and are refractory to aggressive medication therapy and BTX. Deep brain stimulation (DBS) is a reversible, surgical option used for the treatment of primary dystonia including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia or torticollis. DBS is indicated for individuals age seven years and older who do not respond to pharmacotherapy (i.e., medically intractable).


Professional Societies/Organizations: The European Federation of Neurological Society and the Movement Disorder Society-European Section (EFNS/MDS-ES) (Albanese, et al., 2011) task force conducted a systematic literature review and published evidence-based recommendations for the diagnosis and treatment of dystonia. The recommendations stated that pallidal DBS is a good option for primary generalized or segmental dystonia and cervical dystonia following failure of medication or botulinum toxin. In general, pallidal DBS is less effective in secondary dystonia with the exception of tardive dystonia.

In a guidance document for DBS for dystonia, the National Institute for Health and Clinical Excellence (NICE) (United Kingdom) (2006a) stated that the current evidence supports the safety and efficacy of DBS as a treatment modality for dystonia. Dystonia may be treated conservatively or surgically. Conservative treatment only treats the symptoms, and surgical intervention (i.e., thalamotomy and pallidotomy) may not render long-term benefits.

Essential Tremor (ET) and Parkinson Disease (PD)

Essential tremor (ET) is a common movement disorder characterized by postural tremor of the outstretched upper limbs that is absent at rest, not worsened by movement, and not associated with extrapyramidal or cerebellar signs. For most individuals with ET, symptoms can be managed with propanolol and primidone. Alcohol ingestion temporarily reduces ET symptoms, an effect that may last from 30 minutes to several hours. If medications and alcohol ingestion fail to provide adequate relief, patients with severe, chronic and medically intractable ET become candidates for surgical interventions (e.g., thalamotomy and pallidotomy).

Parkinson disease (PD) is a slowly progressive, chronic neurodegenerative disorder resulting from the death of the cells of the substantia nigra which contain dopamine. Eventually, lack of dopamine leads to hyperactivity in the internal globus pallidus (GPI) resulting in direct over stimulation of the GPi and over stimulation of the subthalamic nucleus (STN) which contributes to the existing over stimulation of the GPI.

Levodopa therapy effectively relieves symptoms in approximately 95% of PD patients. However, over the course of 5–10 years, most levodopa-responsive patients manifest increasingly severe and frequent motor fluctuations. When levodopa therapy fails, propanolol can be administered as an adjuvant treatment and anticholinergic medications can counteract symptoms in some patients.

Patients with PD who are considered candidates for DBS include those who have been successfully treated with levodopa, but have become nonresponsive to the medication (i.e., levodopa-resistant). In general, patients who have a significant mental impairment (e.g., dementia, severe depression, affective disorders, psychosis, cognitive deficit) are not considered candidates for DBS. The presence of a significant mental impairment may preclude the ability of the patient to respond to stimulation testing during insertion of the device to assist in proper lead placement and to properly operate the stimulator following insertion. In some cases, it has been reported that DBS may worsen pre-existing mental conditions (e.g., dementia, cognitive deficits/impairment).
Co-morbidities and medical contraindications (e.g., cardiovascular disease, stroke) to implantation are taken into consideration. Surgical contraindications include patients with previous ablative surgery (e.g., thalamotomy, pallidotomy) or conditions that may increase the risk of intracranial hemorrhage (Medtronic, 2014; Benabid, 2009; Olanow, et al., 2009; Pahwa, et al., 2006).


**Professional Societies/Organizations:** In their practice parameters on DBS, the American Society for Stereotactic and Functional Neurosurgery (2011) stated that DBS has been shown to be a safe and effective procedure for medically intractable Parkinson disease and other movement disorders (e.g., moderate to severe medically intractable primary dystonia, tardive dystonia from psychotropic medications) when performed with FDA-approved devices in appropriate medical centers.

In practice parameters for the treatment of PD nonmotor symptoms, the American Academy of Neurology (Zesiewicz, et al., 2010) stated that there was insufficient evidence to support DBS for the treatment of urinary incontinence in PD.

In April 2006, the Quality Standards Subcommittee of the American Academy of Neurology issued an evidence-based practice parameter for the treatment of PD. The report stated that although criteria are evolving, currently patients with PD who are considered candidates for DBS include levodopa-responsive, non-demented and neuro-psychiatrically intact patients who have intractable motor fluctuations, dyskinesia or tremor. According to the subcommittee, DBS of the STN may be considered as a treatment option in PD patients to improve motor function and to decrease motor fluctuations, dyskinesia and medication usage. Patients should be counseled regarding the risks and benefits of this procedure. Insufficient evidence was found to make any recommendations about the effectiveness of DBS of the GPi or Vim nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in patients with PD (Pahwa, et al., 2006).

In interventional procedure guidance on DBS for PD, NICE (2006b) concluded that the current evidence on safety and efficacy appears adequate to support the use of the procedure. NICE also issued a guidance on DBS for tremor and dystonia and found the available evidence adequate to support the use of DBS for tremor that is disabling, interferes with activities of daily living, and is refractory to the highest tolerated doses of medication.

The Quality Standards Subcommittee of the American Academy of Neurology (Zesiewicz, et al., 2011) practice parameter on therapies for ET stated that DBS of the Vim thalamic nucleus is effective in reducing contralateral limb tremor in medically refractory ET. Bilateral DBS is necessary to suppress tremor in both upper extremities, but there are insufficient data regarding the risk-benefit ratio of bilateral versus unilateral DBS in the treatment of ET. Both DBS and thalamotomy are effective in suppressing tremor in ET; however, DBS is associated with fewer adverse events. The decision to use either procedure should be based on each individual's circumstances and risk for intraoperative complications.

**Other Conditions**
DBS has been proposed for the treatment of multiple other disorders including: addictions (e.g., smoking, alcohol); aggressive behavior; Alzheimer disease; anorexia nervosa; camptocormia; cancer; cerebral palsy; cluster headache; chronic pain; central pain from spinal cord injury; depression; epilepsy; Huntington's disease; Lesch-Nyhan syndrome; movement disorders secondary to structural lesions (e.g., basal ganglionic stroke, tumor or vascular malformation); multiple sclerosis tremor; non-Idiopathic Parkinson disease (“Parkinson Plus”); obesity; obsessive-compulsive disorder; restless leg syndrome; short-lasting, unilateral, neuralgiform headache (SUNCT); tardive dyskinesia; tremors of the head and voice; trigeminal neuralgia; trigeminal neuropathy; Tourette syndrome (i.e., Tics); secondary tremors from birth injury, trauma, toxins and stroke; and disorders of consciousness (e.g., minimally conscious, vegetative state) (Taghva, et al., 2012; Lyons, 2011; Nyhan, et al., 2014; Prévinaire, et al., 2009; Larson, 2008; Damier, et al., 2007; Kern and Kumar 2007; Mink, et al., 2006; Skidmore, et al., 2006; Anderson and Arciniegas, 2004; Centers for Medicare and Medicaid [CMS], 2003).
There is insufficient evidence in the published peer-reviewed scientific literature to support DBS for the treatment of any of these conditions. Studies are primarily in the form of case reports and case series with small patient populations (n=2–10) and short-term follow-ups. In some studies, various areas of the brain are used for stimulation and there is a lack of consensus as to which area/areas should be targeted for each condition. Definitive patient selection criteria have not been established. Comparison of DBS to established pharmacotherapy and surgical interventions is lacking. DBS devices are not FDA approved for treatment of these conditions.

**Cerebral Palsy:** Cerebral palsy (CP) is one of the most common causes of secondary dystonia. Approximately 10%–15% of patients develop a dyskinetic movement disorder which starts in early infancy and progresses throughout adulthood. Patients may become severely disabled in their motor function. DBS is a proposed treatment option for those individuals in whom pharmacotherapy is ineffective and/or the side effects limit dosing. There is insufficient evidence to support DBS for CP dyskinesia.

Koy et al. (2013) conducted a systematic review and meta-analysis to evaluate DBS for the treatment of dyskinetic cerebral palsy. Twenty articles consisting of 11 case reports and 19 case series (n=3-14) met inclusion criteria. The analysis included 68 patients who had undergone DBS and outcomes were assessed by the Burke-Fahn-Marsden Dystonia Rating Scale movement (BFMDRS-M) and disability scores (BFMDRS-D). At the 12-month median follow-up, a significant improvement was seen in the postoperative BFMDRS-M (p<0.001) and the BFMDRS-D (p<0.001). The authors noted that the published results were "very variable" and overall, response for secondary dystonia was "far less dramatic" than reported results for primary dystonia. Limitations of the meta-analysis include the low level of evidence, small number of patients, heterogeneity of the procedures and selection of primary DBS target, variable short-term follow-up times with some studies only reporting one post-operative BFMDRS score, and quality-of-life data was only reported in four studies.

**Chronic Pain:** DBS has been proposed for the treatment of various types of chronic, intractable pain. However, because of surgical and nonsurgical treatment interventions, its use has substantially decreased (Kern and Kumar, 2007). Two studies were initiated in the 1980s seeking FDA approval but were prematurely concluded; thus, DBS for the treatment of chronic pain has not received FDA approval (Owen, et al., 2007). Studies are primarily in the form of case series with small patient populations (n=34–56) and short term follow-ups (Owen et al., 2007; Rasche, et al., 2006).

In a meta-analysis, Bittar et al. (2005) found six studies, case series and retrospective reviews, which met inclusion criteria. Follow-up ranged from one month to 15 years. A variety of stimulation sites and methods were utilized. Patients selected for DBS included individuals with pain of known organic origin who failed or poorly tolerated conventional therapies and did not have neuroses/psychoses or severe depression. Twenty-four different pain etiologies (n=1–103) were included (e.g., phantom limb and stump pain, spinal cord pain and/or injury, peripheral neuropathy/radiculopathy, cancer pain and anesthesia dolorosa). The authors reported that DBS was more effective for nociceptive pain than for deafferentation pain (p<0.01). Success rates of up to 80% were reported in patients with low back pain (n=103) and failed back surgery syndrome (n=59).

**Cluster Headache:** A cluster headache is a severe, chronic headache that typically occurs in cyclical patterns (i.e., clusters) on one side of the face at the same time of the day for several weeks. Due to the severity of pain, cluster headaches are often referred to as “suicide headaches.” Treatment options include pharmacotherapy and oxygen administration. DBS has been proposed for the treatment of severe cluster headaches that are refractory to medical management, but there is insufficient evidence in the published peer-reviewed literature to support its effectiveness in this patient population.

Fontaine et al. (2010) conducted a randomized, crossover, double-blind, multicenter study including 11 patients with refractory chronic cluster headaches. Patients were randomized to two, one-month periods of active stimulation vs. sham stimulation separated by a one-week wash-out period. Thereafter, a 10-month open phase was conducted. At the end of the crossover period, there was no significant difference in the frequency of weekly attacks in either group. Following the 10-month open phase, the frequency of the attacks significantly decreased (p=0.08) and patients reported reduced emotional impact. Three “serious” adverse events included an infection requiring removal of the device, loss of conscious with hemiparesia, and severe micturition syncope episodes with hypotension. The study is limited by the small patient population and the short-term follow-up. As
the authors noted, due to the conflicting results in the blinded phase and the open phase additional randomized controlled trials are needed to determine the clinical utility of DBS for cluster headaches.

**Depression:** Depression is an illness characterized by persistent sadness, anxiety, hopelessness, helplessness, pessimism, and a loss of energy and interest in activities. It typically interferes with the activities of daily living and normal functioning (Hauptman, et al., 2008). DBS has been proposed for the treatment of chronic depression nonresponsive to conventional therapies (e.g., behavioural therapies, pharmacotherapy). There is insufficient evidence in the peer-reviewed literature to support DBS for depression. Studies are primarily in the form of small case series (n=15–20) with short-term follow-ups (Lozano et al., 2012; Kennedy, et al., 2011; Malone, et al., 2009; Lozano et al., 2008).

Berlim et al. (2014) conducted a systematic review and meta-analysis to evaluate DBS of the subgenual cingulate cortex (SCC) for treatment-resistant depression. Four observational studies (n=66) met inclusion criteria. Remission rates were 16.7% at three months (n=66), 24.1% at six months (n=66) and 26.3% at 12 months (n=63). Response rates were 36.6% at three months, (n=66), 53.9% at six months (n=66) and 39.9% at 12 months. There was a significant reduction in depression rates between months three and six (p=0.001), but not thereafter. Loss to follow-up at 12 months was 10.8%. In addition, the studies were open label with short-term follow-up and small patient populations. There is insufficient evidence to support DBS of SCC for treatment-resistant depression.

Morishita et al. (2014) conducted a systematic review to evaluate the safety and efficacy of DBS for treatment-resistant major depressive disorder (MDD). A total of 22 clinical trials met inclusion criteria. Five unique DBS approaches using different targets were identified. The targets included nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Only one published controlled trial was found. All studies treated patients with severe, medication refractory MDD, or rarely bipolar disorder and three studies were controlled with sham stimulation. Overall the response rates (percentage of patients with>50% improvement on the Hamilton Depression Rating Scale) ranged from 40%–60%. Most complications were minor surgery-related issues (e.g., superficial infection). Completed suicide and suicide attempts were the most significant adverse events following DBS surgery and happened following DBS with and without stimulation. Several studies excluded patients with suicidal ideation. Limitations of the studies included: small patient populations; heterogeneity of inclusion criteria and outcome measures; duplication of patients across studies. The authors noted that no class I evidence exists in the literature supporting DBS for MDD. The optimal DBS targets are unclear. Therefore, DBS for MDD is considered experimental.

In a Directory Report (2012; reviewed 2013-2015) Hayes reported that there is insufficient evidence to support DBS for treatment-resistant depression. Patient selection criteria, the optimum treatment characteristics and predictors of response have not been established. The overall quality of the evidence is low with lack of randomization and small patient populations.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) (Kennedy, et al., 2009) conducted a systematic review to update 2001 guidelines developed by CANMAT and the Canadian Psychiatric Association for the treatment of adults with major depressive disorders and concluded that DBS was still considered investigational. Seven studies met inclusion criteria. According to the authors, there were no large randomized controlled trials to judge efficacy and consensus on the most effective target brain region for implantation and patient selection criteria have not been established. There was also “no published evidence” on the relative effectiveness of DBS with or without concurrent antidepressant medication in the treatment of this patient population.

**Epilepsy:** Epilepsy is a common condition with repeated seizures caused by abnormal bursts of electrical activity in the brain. Seizures may cause problems with muscle control, movement, speech, vision and/or awareness. DBS of the thalamus, STN, cerebellum, hippocampus, caudate nucleus and mammillary nuclei has been proposed for the treatment of drug-refractory epilepsy. It is also been proposed that individuals who do not respond to vagal nerve stimulation or surgical resection may be DBS candidates. Although improvements in seizures of 70%–80% have been reported, the results have rarely been reproducible. Therefore, DBS for epilepsy is still considered in the experimental stage (Halpern, et al., 2008; Villanueva, et al., 2007).
Appleby et al. (2007) conducted a meta-analysis of 546 relevant articles (i.e., 303 clinical trials, 72 case series, 130 case reports) to “characterize the risks and benefits of DBS and to assess its possible use within the psychiatric setting.” Three percent of the studies included patients with headaches, chronic pain, epilepsy, OCD and depression. Improvements in mentation, mood and behavior were reported in ten studies, six studies reported worsening and two reported no change. An improvement in chronic pain was reported in 26 studies, with no improvement in three studies and worsening of pain in two studies. Improvements in OCD scores were reported in eight studies with one study reporting no differences. Six studies indicated an improvement in anxiety, seven studies included improved cognition, three reported worsening of cognition and improvements in depression. Limitations of the study include the small, heterogeneous patient population and the short-term follow-ups. The authors noted that the possibility of a carryover effect complicating interpretation of the results could not be excluded in four cross-over trials without any washout period. There is insufficient evidence to make firm conclusions regarding safety and efficacy of hippocampal DBS, centromedian thalamic DBS and cerebellar cortical stimulation. Large, well designed randomized controlled trials are needed to validate and optimize the safety and efficacy of invasive intracranial neurostimulation treatments.
in 13 studies cognition was unchanged. Three studies used depression as the primary indicator of treatment outcomes and 34 used depression as a secondary measure. Of the studies evaluating depressive symptoms, an improvement was reported in 83.3% of the studies, 2.7% reported worsening and 14% reported no change. The authors stated that because of the number of studies that did not report on post-DBS mood, the findings of improvement in depressive symptoms should be treated with caution. Following implantation, suicide/attempted suicide and episodes of depression, hypomania and anxiety were reported. Limitations of the studies included: the heterogeneity of the studies, categorical variables (i.e., improvement, no improvement) in outcome measures, lack of outcomes separated by lead placement site, inclusion of case reports and the lack of studies that reported side effects.

**Multiple Psychiatric Disorders:** Nangunoori et al. (2013) conducted a systematic review and meta-analysis in order to better characterize the evidence supporting DBS for major depressive disorder (MDD), obsessive-compulsive disorder (OCD) and Tourette’s syndrome (TS). Studies were included that used a primary, single, standardized outcome scale. A total of 24 studies met inclusion criteria. Four studies were related to MDD (n=48), ten to OCD (n=64) and ten to TS (n=46). Meta-analysis showed that all studies had a clinically detectable and statistically significant reduction in disease-specific outcome scale scores when DBS was used. The average improvement was 2.47 standard deviations for MDD, 2.77 for OCD and 2.97 for TS. Limitations of the studies included the lack of randomized controlled trials, the limited number of studies with small patient populations, short-term follow-ups, and heterogeneity of secondary outcome measures, stimulation parameters and OCD studies.

Lakhan and Callaway conducted a systematic review of clinical trials (n=17), including case series (some with randomization of on/off sessions) and case reports to evaluate outcomes of DBS for the treatment of obsessive-compulsive disorder (OCD) and treatment resistant depression (TRD). Nine OCD studies (n=42 total patients; range, 1–18 per study), seven TRD studies (n=67 total patients; range 1–21 per study), and one study with one patient with both disorders met inclusion criteria. Follow-up ranged from 3–39 months. Due to the sparse data, meta-analysis could not be conducted. The authors noted that the reports of suicide and psychoses following DBS were “disturbing,” and criteria for patient selection and electrode placement need to be established.

**Multiple Sclerosis (MS):** Multiple sclerosis (MS) is a disease of the central nervous system (CNS) that is characterized by areas of demyelination in the white matter of the brain and by recurrent exacerbations of neurologic dysfunction. It is estimated that approximately 10% of MS patients have disabling tremors. Although DBS has been proposed as a treatment option for MS, there is insufficient evidence to support the safety and efficacy of DBS for this condition.

A review by Hayes (2006) of clinical trials that investigated the use of DBS for the treatment of MS tremors included four case series and one nonrandomized controlled trial that compared DBS with thalamotomy. The results suggested that tremor reduction resulted in little or no functional improvement. Only one study reported a statistically significant improvement in one functional outcome. A 2007 update search included a case series with six patients which reported significant improvement in performance of alternating forearm movements during VIM stimulation.

**Obsessive-Compulsive Disorder (OCD):** OCD is a type of anxiety disorder in which individuals have unwanted thoughts (obsessions) and repeated behaviors (compulsions) over and over again. Severe cases of OCD can be disabling and interfere with activities of daily living and relationships. Treatment for OCD may include pharmacotherapy (e.g., selective serotonin reuptake inhibitors [SSRIs] and/or antipsychotic medications) and/or psychotherapy. DBS has been proposed as a treatment option for chronic, severe OCD in individuals who are unresponsive to adequate medical and behavioral therapy including, but not limited to failure of at least three SSRIs (Kuhn, et al., 2010; FDA, 2009; Mallet, et al., 2008).

There is insufficient evidence in the published peer-reviewed literature to support DBS for the treatment of OCD. Studies are primarily in the form of small case series (n=2–16) (Ooms, et al., 2013; Denys, et al., 2010; Okun, et al., 2007; Greenberg, et al., 2006; Rauch, et al., 2006) and case reports.

Alonso et al. (2015) conducted a systematic review and meta-analysis to evaluate DBS for the treatment of obsessive-compulsive disorder. Thirty-one studies (n=116) with small patient populations (n=1–16) met inclusion criteria. Subjects were implanted in striatal areas—anterior limb of the internal capsule, ventral capsule and ventral striatum, nucleus accumbens and ventral caudate (n=83), the subthalamic nucleus (n=27) and in the...
inferior thalamic peduncle (n=6). Ages ranged from 18–75 years and subjects had a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders IV or International Classification of Diseases criteria. Included studies assessed the efficacy of DBS on OCD according to changes on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores (13 studies; n=66) or percentage of responders defined by standardized criteria. Global percentage of Y-BOCS reduction was estimated at 45.1% and global percentage of responders at 60.0%. Data on quality of life was available on 29 patients and various outcome measures were used. No significant differences were detected in efficacy between implant targets. Five patients were lost to follow up. A total of 161 adverse effects were reported and most were considered mild, transient and reversible. Limitations of the studies included: the small patient populations; lack of a comparator; heterogeneity of outcome measures for QOL; heterogeneity of anatomical targeting, electrode design and stimulation parameters; and short duration of sham periods (minutes to three months). The authors also noted that information on OCD symptom dimension, which emerged as one of the clinical predictors of response, was not assessed using specifically designed tools in any study even though it was available for 95 patients. Due to the small number of patients meta-analysis could not be conducted. Clinical predictors of response, response rates and patient selection criteria need to be established.

Kisely et al. (2014) conducted a systematic review and meta-analysis of double-blind randomized controlled trials of DBS vs. sham for the treatment of psychiatric conditions (e.g., OCD, major depression, anorexia nervosa). Five studies met inclusion criteria and all investigated DBS for the treatment of OCD. Data analysis was done on 44 patients. The main outcome was a reduction in obsessive symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Duration of treatment ranged from 2–12 weeks. Patients treated with DBS had a significantly lower mean score (p<0.001), representing partial remission, but one-third of the patients (n=16) experienced significant adverse effects (e.g., intracerebral hemorrhage, infection). There were no differences between the two groups in terms of other outcomes. Two studies reported outcomes for depression and anxiety in OCD patients and no statistically significant differences were seen between DBS and sham (p=0.09). Limitations of the studies included the small patient populations (n=4–16), use of difference DBS target areas in the brain, and short duration of treatment (2–12 weeks). Because all of the subjects had severe treatment-resistant OCD, the result cannot be generalized to patients with less severe symptoms. Meta-analysis could not be conducted. DBS remains an experimental treatment in adults for severe, medically refractory psychiatric conditions.

Kohl et al. (2014) conducted a systematic review to identify and evaluate the effectiveness of different targeted structures in the brain for deep brain stimulation for the treatment of obsessive-compulsive disorder. A total of 25 studies (n=109) that reported five brain stimulation targets met inclusion criteria. Targeted structures included: anterior limb of the internal capsule (n=14), nucleus accumbens (n=37), ventral capsule/ventral striatum (n=29), subthalamic nucleus (n=23) and inferior thalamic peduncle (N=6). Studies were primarily in the form of case reports or small case series (n=3–16). With the exception of one study with a follow-up of 51 months, follow-ups were less than 36 months. Eleven studies had a follow-up of one year or less. Some studies had overlapping patients (n=27). Results were similar regardless of the targeted structure, no superior structure was identified. Some studies reported improvement in symptoms but must be viewed with caution due to the poor methodology of the studies, small patient populations, short-term follow-ups and lack of a comparator.

A multicenter randomized controlled trial by Mallet et al. (2008) compared stimulation of the subthalamic nucleus to sham stimulation in 16 patients, age range 18–60 years, with a primary diagnosis of OCD. Patients were unresponsive to pharmacotherapy (e.g., at least three serotonin-reuptake inhibitors) and cognitive behavioral therapy. The on-off group underwent DBS stimulation followed by sham stimulation and the off-on group underwent sham stimulation followed by DBS stimulation. The stimulation periods involved two 3-month phases (i.e., month 3 to month 6 and month 7 to month 10) separated by a 1-month washout phase. Patients received medications during the trial. Following DBS, a significant decrease was seen in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score (p=0.01). The on-off group had a significantly larger treatment effect than the off-on group (p=0.06). The Global Assessment of Functioning (GAF) score and the Clinical Global Impression (CGI) score were significantly improved after DBS compared to sham (p=0.005, p=0.008, respectively). At the end of the first three months, six (75%) patients were responders based on the Y-BOCS score and eight (100%) were responders based on the GAF scores compared to three (38%) responders following sham. No significant differences following DBS or sham were seen in the scores on the Montgomery and Asberg Depression Scale (MADRS), the Brief Scale for Anxiety, and the Sheehan Disability Scale. Due to the adverse events (i.e., intracerebral hemorrhage, infections requiring removal of the electrode) the authors stated that the benefits
should be weighed carefully against the risks. Author-noted limitations included the variable deep brain stimulation settings used, small patient population and short duration of the study.

The American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and Endorsed by the CNS and American Association of Neurological Surgeons (Hamani, et al. 2015) conducted a systematic review of the literature to develop guidelines for DBS for OCD. Six studies met inclusion criteria. The authors reported the following regarding the treatment of medically refractory OCD: (1) one study (n=16) supported bilateral subthalamic nucleus DBS; (2) one study (n=14) supported bilateral nucleus accumbens DBS and one study (n=10) reported no difference in DBS on/off scores; (3) evidence was insufficient to support unilateral DBS. It was noted that the most effective target for DBS, patient selection criteria and predictors for the best prognosis have not been established.

In their practice guideline for the treatment of OCD, the American Psychiatric Association (2013) described DBS as a “less-well-supported” monotherapy that may be considered after first and second-line therapies have been exhausted but clarify that there is little supporting evidence (e.g., “few small trials or case reports or uncontrolled case series”). DBS has been reported to show efficacy in individuals with severe, highly treatment-resistant OCD, but the procedure is not without its risk.

**Tardive Dyskinesia:** Tardive dyskinesia is a neurological syndrome characterized by repetitive, involuntary, purposeless movements and caused by the long-term use of neuroleptic drugs. Additional features may include grimacing; tongue protrusion; lip smacking, puckering and pursing; rapid eye blinking; and rapid movements of the arms, legs, and trunk.

In a prospective phase two multicenter study, Damier et al. (2007) investigated DBS in patients with severe TD refractory to medical management (n=10). Patients had been treated with antipsychotic medication for depression, schizophrenia or childhood disintegrative disorder. At the six-month follow-up, a double-blind evaluation resulted in successful outcomes by a decrease in the Extrapyramidal Symptoms Rating Scale, including choreic movements and dystonia score, by more than 40% (p=0.05). A significant decrease in the Abnormal Involuntary Movement Scale score (p=0.006) was also reported.

**Tourette Syndrome (Tics):** Tourette syndrome (TS), also known as chronic motor tic, chronic multiple tics, Gilles de la Tourette's disease or syndrome (GTS), habit spasms, maladie de tics, and paulitis tics, is a chronic neuropsychiatric disordered characterized by motor (e.g., repetitive involuntary movements of the face, head, upper body) and phonic, or vocal (e.g., sniffing, grunting, barking) tics. TS is often associated with behavioral abnormalities such as attention-deficit hyperactivity disorder and OCD. The waxing and waning characteristics of tics makes it difficult to investigate the safety and efficacy of DBS. It has been proposed for patients who have not received adequate benefit from behavioral therapy and pharmacotherapy. Current studies include small patient populations, and the optimal DBS target for these individuals has not been defined (Cannon, et al., 2012; Kuhn, et al., 2010; Ackermans, et al., 2008; Mink, et al., 2006).

Piedad et al. (2012) conducted a systematic review to determine which patients with Tourette syndrome (TS) should be treated with DBS and the best target areas for electrode placement. Thirty-six studies met inclusion criteria including case reports, three case series and three randomized controlled trial. Based on the available data, the authors noted that it was "suggested" that the best candidates are patients with significant functional impairment due to tic symptoms and are nonresponsive to conventional pharmacotherapy and behavioral interventions. The globus pallidus internus and thalamus appeared to be the safest and most effective targets, especially for patients with “pure” TS and patients with comorbid obsessive-compulsive symptoms, anxiety and depression. There is a lack of consensus on treatment-refactoriness and large randomized controlled trials are needed to establish patient selection criteria and the appropriate target areas for placement.

The European Society for the Study of Tourette Syndrome (ESSTS) (Muller-Vahl, et al, 2011) conducted a systematic review of the literature to evaluate DBS for the treatment of Tourette syndrome (TS). Twenty four studies (n=63) including three randomized controlled trials, 18 case reports and three case series were reviewed. ESSTS concluded that DBS should only be used in “treatment resistant and severely affected adults” and “highly” recommended that it be in the context of controlled clinical trials.

The Tourette Syndrome Association (Mink, et al., 2007) convened a group of TS and DBS experts to develop guidelines for the early use and potential clinical trials of DBS for the treatment of TS believing that investigation
of DBS for TS was justified due to the success of DBS with other disorders. The subgroup stated that although DBS has the potential to be an effective therapy for a carefully selected subgroup of TS patient’s “there are many unknowns about the potential applications” of DBS and investigation is warranted.

**Responsive Cortical Stimulation**

Closed-loop, responsive cortical stimulation involves the implantation of electrodes which are connected to a generator that provides electrical stimulation to specific areas of the brain in response to abnormal brain activity. This technology is different from an open-loop or nonresponsive technique (e.g. deep brain stimulation) which delivers a continuous or intermittent electrical stimulation at programmed intervals. Closed-loop, responsive cortical stimulation is supported by the published peer-reviewed literature as an adjunctive treatment option for a carefully identified subpopulation of patients with medically refractory partial epilepsy and are not candidates for surgery or for vagal nerve stimulation (Heck, et al., 2014; Fridley et al., 2012; Morrell, et al., 2011; Skarpaas and Morrell, 2009).

Epileptic seizures are classified as partial or generalized depending on whether they begin focally at one or two points in the brain (i.e., a partial-onset seizure) or bilaterally with multiple foci (i.e., a generalized seizure). Standard therapy includes antiepileptic medication, vagal nerve stimulator and/or surgical removal of seizure focus. Partial seizures can generalize secondarily and result in tonic-clonic activity in which the person loses consciousness accompanied by muscle stiffness and jerking movements. In a subset of patients with medically refractory partial epilepsy, electrical cortical stimulation has been proposed as an adjunctive therapy to pharmacotherapy. There is currently one FDA approved device for this indication RNS is proposed to detect abnormal electrical activity in the brain and deliver electrical stimulation that will normalize the brain activity before the patient has a seizure.

The RNS® System (NeuroPace, Inc. Mountain View, CA) is a responsive cortical stimulation closed-loop system. It is proposed as a treatment option for patients who have medically refractory partial epilepsy with partial onset seizures, are refractory to two or more antiepileptic medications and have one of the following seizure types: 1) simple partial motor: seizures characterized by alteration in motor function without change in awareness; 2) complex partial: seizure includes impairment in awareness and/or 3) generalized tonic, clonic or tonic-clonic seizures. RNS is not indicated for the treatment of generalized epilepsies in which seizures arise from all areas of the brain at the same time.

The system includes an implantable RNS® neurostimulator, a Depth Lead (implanted within the brain) and a NeuroPace® Cortical Strip Lead (implanted on the brain surface). Each lead contains four electrodes. The leads to be implanted are selected based on the location of the seizure focus: subdural cortical, depth, or a combination of the two. The Cortical Strip Leads are recommended for seizure onsets on the surface of the cortex, where the lead can be placed over the focus. The Cortical Strip Leads come in three lengths and are implanted through a craniotomy. The Depth Leads are recommended for seizure onsets beneath the cortical surface (e.g., within the mesial temporal lobe, within subcortical lesions) where the lead can be placed within the seizure focus. Depth Leads come in four different configurations. These leads may be implanted using stereotactic techniques through a burr hole in the skull. The leads are placed at the seizure focus as determined by radiologic imaging, presurgical electroencephalogram (EEG) recordings, or phase II subdural electrocorticogram (ECoG) monitoring. The neurostimulator is a programmable, battery powered, microprocessor-controlled device that delivers a short train of electrical pulses to the brain through the implanted leads. The neurostimulator is implanted in the cranium flush with the skull, is extradural and does not come in contact the brain. Up to four leads may be implanted with only two leads connected to the neurostimulator at any given time. Once in place, the neurostimulator is covered by the scalp.

External components of the system include the programmer, laptop computer with software and a Wand that allows remote monitoring of brain activity. The Wand is used to retrieve stored data from the neurostimulator. Using the programmer, the physician programs the initial setting and makes follow-up adjustments as needed based on brain activity and response to stimulation. The typical patient receives brief bursts (100–200 msec) of high-frequency stimulation with a total cumulative stimulation time of less than six minutes a day. The programmer also allows visualization of the patient's brain electrical activity (electrocorticogram [ECoG]) in real-time and the ability to upload the patient's ECoGs stored in the RNS neurostimulator. The patient is provided a magnet that is swiped over the neurostimulator to record brain activity during a seizure. This activity enables the physician to identify the event during data review. The magnet can also be used to temporarily stop stimulation.
The neurostimulator has to be replaced every 2.0–3.7 years when the battery reaches its end of service. If the existing leads are functioning properly and there are no problems, the same leads will be connected to the new stimulator. It is recommended that the leads not be removed if the stimulation is not successful due to potential damage to brain tissue.

**U.S. Food and Drug Administration (FDA)**

The RNS System (NeuroPace, Inc. Mountain View, CA) is FDA approved by the premarket approval (PMA) application process. The device is indicated “as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than two epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/or secondarily generalized seizures). The RNS System has demonstrated safety and effectiveness in patients who average three or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures”. Exclusion criteria in the FDA clinical trial included subjects who did not have an implanted vagus nerve stimulator or an implanted device that delivers electrical energy to the head, had not had surgery for the treatment of epilepsy within the preceding six month, and had not been diagnosed with active psychosis, severe depression or suicidal ideation in the preceding year. If subject had a VNS, it must have been explanted (excluding leads) prior to or at the time of RNS implantation. VNS must have been discontinued for at least three months prior to enrollment (FDA, 2013).

Continued approval of the PMA is contingent upon the submission of yearly reports including model number, number of devices sold and distributed. Also, NeuroPace must conduct and report on a long-term treatment study to establish safety (adverse event rates) and effectiveness (average disabling seizure frequency) through seven years. Successful responder rate is defined as sustained ≥ 50% reduction in total disabling seizures from baseline. Quality of life will also be measured.

**Literature Review**

Bergey et al. (2015) reported on the ongoing seven-year, multi-center study assessing the efficacy and safety of patients with RNS implantation who were involved in the Morrell et al. (2011) and Heck et al. (2014) studies and transitioned to this open-label study. A total of 230 participants transitioned into this ongoing 7-year study and data on 191 are reported herein. Adverse events and daily seizure diary data were collected at least every six months. Quality of life was assessed yearly by the Quality Of Life In Epilepsy Inventory–89 (QOLIE-89). Efficacy was assessed as median percent change in seizures and as responder rate (the percentage of participants with a 50% or greater reduction in seizures) for each 3-month period compared to the preimplant baseline. Antiepileptic medications were adjusted as medically necessary. The mean and median follow-up was 5.4 patient implant years (range 5 weeks–9.6 years). The median percent reduction in seizures was 60% at the beginning of year three and 66% at the beginning of year six and the responder rates were 58% and 59%, respectively. The last three months of data showed 84% of participants (207/247) had some improvement, 60% (146/247) had a 50% or greater reduction (compared to 8% [19/247] with a 50% or greater increase), and 16% of participants (40/247) were seizure-free. Sixty-three percent of responders and 70% of nonresponders had a new antiseizure medication added, and 9% of the responders and 8% of the nonresponders had a reduction in the number or dosage of antiseizure medications. Statistically significant improvements in quality of life were maintained (p<0.05). The most common serious device related adverse events over the mean 5.4 years of follow-up were implant site infection (9.0%) involving soft tissue and neurostimulator explantation (4.7%).

Cognitive impairment is a well-recognized comorbidity of medically intractable partial seizures. Loring et al. (2015) conducted an analysis of neuropsychological data collected from Morrell et al. (2011) and Heck et al. (2014) multicenter, double-blind, randomized controlled trial (n=175) which assessed the safety and efficacy of the RNS system for adults with medically intractable and disabling partial-onset seizures arising from one or two seizure foci. Language and verbal memory were identified as the primary cognitive outcomes. Primary neuropsychological tests included the Boston Naming Test (BNT) and the Rey Auditory Verbal Learning Test (AVLT). The change in neuropsychological outcome measures from baseline through two years was assessed. Seizures were recorded in seizure diaries. No significant cognitive declines were reported on any neuropsychological outcome measure. Significant improvements were present for naming (BNT), with 23.5% of subjects demonstrating reliable change indices (RCIs) improvements and 6.7% demonstrating declines. There were statistically significant improvements in verbal learning on the AVLT, with 6.9% of subjects demonstrating RCI improvements and 1.4% demonstrating declines. There was a significant overall memory improvement...
Morrell et al. (2011) conducted a multicenter, double-blind, randomized controlled pivotal trial (n=191) to assess the safety and effectiveness of responsive cortical stimulation using the RNS System as an adjunctive therapy for the treatment of medically refractory seizures. Patients were age ≥ 18 years, had partial onset seizures that were not controlled with two or more trials of antiepileptic drugs (AEDs), had three or more disabling seizures per month on average, and had undergone standard diagnostic testing that localized seizures in one or two regions.

Patients had an increased frequency of seizure severity and/or duration which resulted in hospitalization for an event for which detection of epileptiform activity continued beyond a preset physician-defined duration and saturations (an event with amplitudes exceeding amplifier sensitivity) for a maximum total of 200 events stored during the 84-day sampling period. ECoG recordings were grouped by interrater results into (1) those that both reviewers identified as electrographic seizures; (2) those that both identified as nonepileptic seizures; and (3) those that one reviewer ranked as electrographic seizure and the other as nonepileptic seizure.

Five reviewers forming five pairs reviewed the recordings. The overall agreement rate (both reviewers of each pair agreed “seizure” or “not seizure”) was 79%, with a range from 0.38–0.70. The median intrapatient agreement rate was 94%, (i.e., 50% of patients had interrater agreement rates of 94% or better). Most patients generally had unambiguous detections that could reliably be categorized as electrographic seizure or as nonictal epileptiform activity. A minority of patients accounted for agreement rates <75% which meant that programming parameters allowed recording of activity that could be reliably interpreted in the majority.

In 2014 Heck et al. published the final two-year results (n=191) of the RNS pivotal trial described below (Morrell, et al., 2011). Seizure reduction increased over the first two years and was sustained at around 50%. At two years following implantation the median reduction in seizures in the open label period was 53% which was a significant reduction compared to baseline (p<0.001). The responder rate at two years was 55%. The continued improvement during the open period reached statistical significance for both the median percent reduction and the responder rate (p<0.0001). During the last three months of available data, changes in AEDs did not affect the favorable response from RNS. Eight-two percent of subjects had some improvement in seizure frequency, 54% had ≥50% reduction in seizures and 7% had a greater increase in seizures. Quality of life was statistically significant at end of year one and two (p<0.05 ea.) at one year and two years following implantation. Regarding mood, there were no adverse changes in in mood or in suicidality on the BDI-II score or in the POMS scores at years one and two.

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Meador et al (2015) prospectively reported on the quality of life (QOL) and mood surveys administered to patients (n=191) treated with RNS in the Morrell, et al. (2011) and Heck et al. (2014) randomized controlled trial. Surveys were administered at baseline, at the end of the four-month blinded period, and at the end of year one and year two of the open label period. Compared with baseline, QOL improved in both groups at the end of the blinded period and at the year one and year two follow-ups. At two years, 44% of patients reported meaningful improvements in QOL and 16% reported a decline in QOL. There were statistically significant group improvements on every composite subscale (Epilepsy-Targeted, Cognitive, Mental Health, and Physical Health; p<0.05 ea.) at one year and two years following implantation. Regarding mood, there were no adverse changes in in mood or in suicidality on the BDI-II score or in the POMS scores at years one and two.

Quigg et al. (2015) conducted a retrospective review of a randomized controlled trial (Morrell, et al., 2011; Heck et al., 2014) to quantify the interrater reliability in the classification of electrocorticographic (ECoG) recording events (n=7221 events) from patients (n=128) implanted with RNS. The numbers of ECoG recordings from each patient varied with detection parameters, the nature of the EEG pattern, and the frequency with which patients transferred the data. The ECoG recordings reviewed were the first 100 most recent long episodes (an event for which detection of epileptiform activity continued beyond a preset physician-defined duration) and saturations (an event with amplitudes exceeding amplifier sensitivity) for a maximum total of 200 events stored during the 84-day sampling period. ECoG recordings were grouped by interrater results into (1) those that both reviewers identified as electrographic seizures; (2) those that both identified as nonepileptic seizures; and (3) those that one reviewer ranked as electrographic seizure and the other as nonepileptic seizure. Five reviewers forming five pairs reviewed the recordings. The overall agreement rate (both reviewers of each pair agreed “seizure” or “not seizure”) was 79%, with a range from 0.38–0.70. The median intrapatient agreement rate was 94%, (i.e., 50% of patients had interrater agreement rates of 94% or better). Most patients generally had unambiguous detections that could reliably be categorized as electrographic seizure or as nonictal epileptiform activity. A minority of patients accounted for agreement rates <75% which meant that programming parameters allowed recording of activity that could be reliably interpreted in the majority.
epileptogenic regions. The primary outcome was the reduction in the mean seizure frequency during blinded evaluation period (BEP) at 12 weeks postimplantation. The second primary outcome was the comparison of serious adverse events to adverse events from historical data from comparable procedures. Responders were those subjects with a ≥ 50% reduction in seizures. Disabling seizures included simple partial motor, complex partial, and secondarily generalized tonic-clonic seizures. The Quality of Life in Epilepsy (QOLIE-89) inventory, and four neuropsychological testing and mood inventories including the Beck Depression Inventory (BDI-II) 5, and the Center for Epidemiologic Studies Depression Scale (CES-D) 6 were used to measure secondary outcomes. Antiepileptic drugs (AEDs) were to be held constant through the BEP and then could be adjusted as needed. Patients underwent implantation of the RNS system followed by a one month break-in period without stimulation. Thereafter, patients were randomization to RNS cortical stimulation (n=97) or sham (n=94). Patients recorded their daily seizure activity. During the first month postimplant, both groups experienced seizure reduction but the reduction wasn't sustained in the sham group. Mean seizure frequency was significantly reduced in the RNS group (p=0.012) during the BEP and the RNS group had significantly fewer days with seizures than the sham group (p=0.048). At twelve weeks postimplant, the sham patients transitioned to RNS stimulation for an 84-week open-label period. During the open-label period, the seizure reduction was sustained in the treatment group and significantly reduced in the sham group (p=0.04). There were significant improvements in overall quality of life scores in both groups and no deterioration in mood or neuropsychological function during BEP or after BEP. The difference between the two BEP groups was not significant. The responder rate at one year postimplant was 43% (n=177) and 46% at two-year postimplant (n=102). Thirteen subjects (7.1%) were seizure-free over the most recent three-month period at the data cutoff point. Six patients required changes in AEDs before the end of the BEP. Serious adverse events over the first 28 days were not worse than events reported in the literature for comparable procedures and not significantly different between the RNS group and sham group. Adverse events included: 4.7% Intracranial hemorrhages (9/191), 5.2% infections (10/191) with four explantations, four sudden unexplained death in epilepsy (three had been explanted). Compared to preimplant 52.7% of subjects had verbal memory dysfunction and 56.2% had visuospatial memory dysfunction. Limitations of the study include the small patient population, short-term follow-up; AEDs were adjusted in six patients prior to end of BEP, and number of patients lost to follow-up.

**Motor Cortex Stimulation**

Motor cortex stimulation (MCS), also referred to as cerebral cortex stimulation or extradural motor cortex stimulation (EMCS), is primarily proposed for relief of refractory neuropathic pain and involves implantation of epidural electrodes in the cerebral cortex. Although the exact mechanism of MCS is unknown, it has been hypothesized that it may induce the release of endogenous opioids in various brain structures, resulting in pain relief (Cheng and Eskandar, 2010; Maarrawi, et al., 2007).

Typically, temporary placement of a MCS device is performed to determine if the device will relieve the pain. If the patient consistently (e.g., 3–14 days) experiences at least a 50% reduction in pain, a second surgery is performed to permanently connect the electrodes and implant the programmable device under the skin near the collarbone. Image-guided localization (e.g., magnetic resonance imaging [MRI], functional MRI [fMRI], computerized tomography) and intraoperative mapping using somatosensory evoked potential (SSEP), intraoperative stimulation of the cortex, and/or neuronavigation are used to locate the precise placement of the electrodes, which is critical for successful pain relief. Electrodes are introduced through a burr hole or frontoparietal craniotomy into the protective layer covering the motor cortex area (epidural) of the brain, placed over the targeted area and connected to a programmable pulse generator. The lead wire from the programmable device goes up the back of the neck under the scalp to the electrodes (Cheng and Eskandar, 2010; Levy, et al., 2010; Arle and Shils, 2008).

Because MCS is a less invasive procedure than other invasive surgical procedures such as DBS, it is proposed to be a safer procedure with less serious complications. MCS has been proposed for treatment when invasive procedures have failed or when patients are not appropriate candidates for an invasive procedure. Some proponents of MCS report that MCS is less harmful than long-term opioid use. However, serious complication including intracranial bleeding; infection; permanent neurological deficits; and seizure activity, especially during programming and reprogramming of the MCS device, have been reported (Cheng and Eskandar, 2010; Levy, et al., 2010; Maarrawi, et al., 2007).

MCS was initially used for the treatment of medically refractory central pain syndrome following ischemic or hemorrhagic stroke and facial neuralgias (e.g., trigeminal neuralgia, postsurgical trigeminal deafferentation such
as anesthesia dolorosa, postherpetic neuralgia). However, its use has been proposed for the treatment of other conditions including: neuropathic pain following spinal cord injuries (e.g., supraspinal pain after hemorrhage and infarction), post-stroke pain, chronic pain, amyotrophic lateral sclerosis (ALS), thalamic pain syndrome, plexus avulsion, dysphagia, Parkinson disease, dystonia, spasticity, multiple sclerosis, chronic regional pain syndrome (CRPS), phantom limb pain, epilepsy and peripheral nervous system lesions. MCS has also been used for intraoperative monitoring (Tanei, et al., 2011; Cheng and Eskandar, 2010; Levy, et al., 2010; Fontaine, et al., 2009; Prévinaire, et al., 2009; Arle and Shils, 2008).

U.S. Food and Drug Administration (FDA)
There are no devices approved by the FDA for motor cortex stimulation.

Literature Review
There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of MCS for any indication. Studies are primarily in the form of case reports and case series with small heterogeneous patient populations (n=3–10) and short-term follow-ups. Outcomes regarding the benefits of MCS are conflicting. Some studies reported that the initial pain relief following MCS was not sustained over time and in some cases, worsening of pain followed MCS. Surgical techniques, electrode placement, device programming, outcome measures and patient selection criteria have not been established.

Fontaine et al. (2009) conducted a systematic review to evaluate the safety and efficacy of MCS for the treatment of chronic neuropathic pain. Fourteen studies (n=210), case series and retrospective reviews, met inclusion criteria. Reported mean follow-up was 30.5 months (range, several weeks to ten years). Overall, 56.7% of patients reported a 40%–50% (good) improvement in pain. Sixty-nine patients with ≥ 1 year follow-up reported a good response, and in two studies with 49-month follow-up, 47% and 22.6% of patients reported good results. The reported Visual Analog Scale scores for 76 patients reflected an average 56.6% improvement in postoperative scores. The most common adverse events were intraoperative or trial stimulation period seizures, infections and hardware-related problems. The authors stated that these results should be viewed with caution due to the limited number of studies that were primarily retrospective study designs with heterogeneous small patient populations (n=3–31). Short-term follow-up, loss of efficacy and the variable surgical techniques, stimulation settings and electrode placement were other noted limitations.

A limited number of randomized controlled trials have evaluated the use of MCS for the treatment of neuropathic pain comparing outcomes of on/off stimulation. In a crossover trial, Lefaucheur et al. (2009) reported that patients with trigeminal neuralgia (n=4), brachial plexus lesion (n=4), neurofibromatosis type-1 (n=3), upper limb amputation (n=2), herpes zoster ophthalmicus (n=1), atypical orofacial pain secondary to dental extraction (n=1), and traumatic nerve trunk transection in a lower limb (n=1) did not experience sustained pain relief during the crossover phase of the trial. Of the 12 patients who participated in the open study phase, 60% reported a mean pain relief of 48% on Visual Analog Scale scores at 12 months follow-up. In a study involving 11 patients (Velasco, et al., 2008) with chronic deafferentation pain syndromes (n=11), three patients reported no improvement following a temporary trial of MCS. The remaining patients who underwent permanent implantation reported a significant reduction in pain (p<0.01) during the one-year follow-up. The authors stated that “given the heterogeneous information that one gathers from the literature on MCS, it is impossible at present to draw a conclusion concerning candidates for this treatment.”

Use Outside of the US
In their guidelines on neurostimulation for neuropathic pain, the European Federation of Neurological Societies (EFNS) (Cruccu, et al., 2007) stated that the literature primarily consisted of case series including patients with central post-stroke pain (CPSP) (n=20 case series with much overlap; 143 non-overlapping patients) and facial neuropathic pain (n=8 case series; 60 patients). Success rates ranged from 0%–100% for CPSP and 43%–100% for facial pain. Most studies did not have comparators, and outcome and treatment assessments were dissociated. Only case reports were found on patients with phantom pain, brachial plexus, nerve trunk lesion, spinal cord lesions and complex regional pain syndrome (CRPS). Based on these studies, EFNS stated that “MCS is useful in 50–60% of patients with CPSP and central or peripheral facial neuropathic pain, with small risk of medical complications,” but the evidence was insufficient to support MCS for any other condition.

Summary
Professional societies and evidence in the published peer-reviewed scientific literature support DBS for the
treatment of a carefully selected subset of individuals with chronic, medically intractable primary dystonia,
essential tremor (ET), and Parkinson disease (PD).

Studies investigating DBS for the treatment of all other disorders are primarily in the form of case reports and
case series with small, heterogeneous patient populations and short-term follow-ups. Patient selection criteria,
targeted areas in the brain, and appropriate stimulation systems have not been defined, nor have studies
compared DBS to established pharmacotherapy or surgical interventions. The evidence in the published peer-
reviewed scientific literature does not support DBS for any of the following conditions (list may not be all
inclusive):

- cerebral palsy
- central pain from spinal cord injury
- cluster headaches
- chronic pain
- depression
- epilepsy
- Huntington’s disease
- Lesch-Nyhan syndrome
- movement disorders secondary to structural lesions (e.g., basal ganglionic stroke, tumor or vascular
  malformation)
- multiple sclerosis tremors
- non-idiopathic Parkinson disease (“Parkinson Plus”)
- obsessive-compulsive disorder
- Tourette syndrome (Tics)
- tardive dyskinesia
- tremors of the head and voice
- tremors from birth injury, trauma, toxins, and stroke

The published peer-reviewed literature supports the use of responsive cortical stimulation (e.g., NeuroPace®
RNS® System) for the treatment of a select subgroup of patients with medically refractory partial seizures who
are not candidates for vagal nerve stimulation or surgical intervention.

There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and
efficacy of motor cortex stimulation (MCS) for any indication. Studies are primarily in the form of case reports
and case series with heterogeneous, small patient populations and short-term follow-ups. The studies used
various outcome measures and results were conflicting. Criteria for patient selection, surgical techniques,
electrode placement and device programming have not been established. There is no US Food and Drug
Administration approved device for MCS.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible
   for reimbursement.

Deep Brain Stimulation

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61863</td>
<td>Twist drill, burr hole, craniotomy, or cranieotomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative</td>
</tr>
</tbody>
</table>
Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)

Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array

Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)

Revision or removal of intracranial neurostimulator electrodes

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

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

Revision or removal of cranial neurostimulator pulse generator or receiver

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<td>C1767</td>
<td>Generator, neurostimulator (implantable), nonrechargeable</td>
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<tr>
<td>C1778</td>
<td>Lead, neurostimulator (implantable)</td>
</tr>
<tr>
<td>C1787</td>
<td>Patient programmer, neurostimulator</td>
</tr>
<tr>
<td>C1816</td>
<td>Receiver and/or transmitter, neurostimulator (implantable)</td>
</tr>
<tr>
<td>C1820</td>
<td>Generator, neurostimulator (implantable), with rechargeable battery and charging system</td>
</tr>
<tr>
<td>C1883</td>
<td>Adaptor/extension, pacing lead or neurostimulator lead (implantable)</td>
</tr>
<tr>
<td>C1897</td>
<td>Lead, neurostimulator test kit (implantable)</td>
</tr>
<tr>
<td>L8679</td>
<td>Implantable neurostimulator, pulse generator, any type</td>
</tr>
<tr>
<td>L8680</td>
<td>Implantable neurostimulator electrode, each</td>
</tr>
<tr>
<td>L8681</td>
<td>Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only</td>
</tr>
<tr>
<td>L8682</td>
<td>Implantable neurostimulator radiofrequency receiver</td>
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<tr>
<td>L8683</td>
<td>Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver</td>
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<tr>
<td>L8685</td>
<td>Implantable neurostimulator pulse generator, single array, rechargeable, includes extension</td>
</tr>
<tr>
<td>L8686</td>
<td>Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension</td>
</tr>
<tr>
<td>L8687</td>
<td>Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension</td>
</tr>
<tr>
<td>L8688</td>
<td>Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension</td>
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Responsive Cortical Stimulation

Covered when medically necessary:

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<td>61850</td>
<td>Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical</td>
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<tr>
<td>61860</td>
<td>Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical</td>
</tr>
<tr>
<td>61863</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of</td>
</tr>
</tbody>
</table>
neurostimulator electrode 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 with stereotactic implantation of neurostimulator electrode 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)

61880 Revision or removal of intracranial neurostimulator electrodes

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

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

61888 Revision or removal of cranial neurostimulator pulse generator or receiver

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<td>Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension</td>
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**Motor Cortex Stimulation**

Experimental/Investigational/Unproven/Not Covered when used to report motor cortex stimulation:

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<td>61885</td>
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