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Deep Brain Stimulation

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Last Review
04/17/2025
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Review History

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Scope of Policy

This Clinical Policy Bulletin addresses deep brain stimulation.

I. Medical Necessity

A. Aetna considers unilateral or bilateral deep brain stimulators (e.g., stimulation of the ventral intermediate thalamic nucleus, globus pallidus, and subthalamic nucleus) medically necessary durable medical equipment (DME) for the treatment of intractable tremors as a consequence of Parkinson's disease or essential tremor when *all* of the following criteria are met:

- Member does not have dementia, severe depression, cerebral atrophy, or Hoehn and Yahr stage V Parkinson's disease (see Note below) *, *and*
- Member does not have other independent diagnoses that could explain the failure to respond to medical treatment, *and*
- Member suffers from disabling upper extremity essential tremor that is not responding satisfactorily to drug therapy or suffers from a disabling tremor of idiopathic Parkinson's disease that is refractory to pharmacotherapy, *and*
- There is no focal lesion of the basal ganglia (e.g., a space occupying lesion or lacunae) at the target site that would negate the result of thalamic stimulation, *and*
- There is sufficient residual motor function in the upper extremity so that it is reasonable to expect an improvement following the surgery.

*__Note__: Hoehn and Yahr Stage V individuals exhibit the following characteristics:

- Cachectic state
- Cannot stand or walk (need wheelchair assistance, or are unable to get out of bed
- Invalidism
- Requires constant nursing care.

B. Aetna considers unilateral or bilateral deep brain stimulators (e.g., stimulation of the globus pallidus and subthalamic nucleus) medically necessary DME for the treatment of severe, refractory motor complications of Parkinson's disease when *all* of the following criteria are met:

- A minimal score of 30 points on the motor portion of the United Parkinson's Disease Rating Scale (UPDRS) when the member has been off medication for about 12 hours (scores on this scale range from 0 to 108; higher values indicate greater severity of symptoms); *and*
- Member does not have dementia, severe depression, cerebral atrophy, or advanced (Hoehn and Yahr stage V) Parkinson's disease; *and*

- Member is levodopa responsive with clearly defined "on" periods; *and*
- Motor complications that can not be managed with medication; *and*
- Presence of at least 2 major symptoms of Parkinsonism (e.g., tremor, rigidity, and bradykinesia).

C. Aetna considers unilateral or bilateral deep brain stimulators (e.g., stimulation of the globus pallidus and subthalamic nucleus) medically necessary DME for the treatment of persons 7 years of age or older with intractable primary dystonia, including generalized and/or segmental dystonia, hemidystonia and cervical dystonia.

D. Aetna considers bilateral stimulation of the anterior nucleus of the thalamus (e.g., the Medtronic DBS System for Epilepsy) medically necessary for adults aged 18 years or older who have partial onset seizures with or without secondary generalization to tonic-clonic activity, and have not responded to 3 or more antiepileptic medications. (Note: This approach is for individuals who averaged 6 or more seizures per month during the previous 3 months, with no more than 30 days between seizures. It hasn't been evaluated in persons whose seizures are less frequent).

E. Aetna considers brain magnetic resonance imaging (MRI) with or without contrast medically necessary for pre-operative planning or intra-operative navigation for implantation of deep brain stimulator.

Note: The average battery life of a non-rechargeable stimulator is 3 to 5 years, depending upon how much stimulation the individual receives each day. Rechargeable neurostimulators last longer, about 9 years. The neurostimulator would then need to be replaced as an outpatient procedure, but the leads implanted to the brain do not need to be replaced.

Note: Placement of fiducials (e.g., WayPoint anchor) for implantation of deep brain stimulator (DBS) is considered integral to DBS lead implantation and is not reimbursed separately.

II. Experimental, Investigational, or Unproven

The following procedures are considered experimental, investigational, or unproven because the effectiveness of these approaches has not been established:

A. Deep brain stimulation (DBS) for tremor from other causes such as trauma, multiple sclerosis (MS), degenerative disorders, metabolic disorders, infectious diseases, and drug-induced movement disorders.

B. DBS is considered experimental, investigational, or unproven for the following indications (not an all inclusive list), because there is insufficient evidence to support its effectiveness for these indications:

- Alzheimer's disease
- Anorexia nervosa
- Autism spectrum disorder
- Blepharospasm
- Cerebral palsy
- Chemical dependency disorder (e.g., alcohol, cocaine, nicotine, opioids and psychostimulants)
- Chorea-acanthocytosis
- Chronic cluster headache
- Chronic pain syndrome including complex regional pain syndrome/reflex sympathetic dystrophy
- Chronic vegetative state
- Depression
- Disorders of consciousness (e.g., minimally conscious state, unresponsive wakefulness syndrome, and vegetative state)
- Dystonia and spasticity secondary to anoxic brain injury
- Explosive aggressive behavior
- Head or voice tremor
- Huntington's disease
- Movement disorders after stroke
- Obesity
- Obsessive-compulsive disorder
- Orthostatic tremor
- Parkinson’s disease-related camptocormia, dysarthria/speech deficits, postural instability, restless

legs syndrome, and gait disorders (e.g., gait instability and freezing of gait)
- Post-traumatic tremor
- Postural trunk deformities
- Self-injurious behavior
- Status dystonicus
- Substance use disorders
- Tinnitus
- Tourette syndrome
- Traumatic brain injury.

III. Related Policies

- CPB 0153 - Thalamotomy (../100_199/0153.html)
- CPB 0307 - Parkinson's Disease (../300_399/0307.html)

CPT Codes / HCPCS Codes / ICD-10 Codes

Code	Code Description
CPT codes covered if selection criteria are met:	
61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
61863	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; first array
+ 61864	each additional array (List separately in addition to primary procedure)

Code	Code Description
61867	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), with use of intraoperative microelectrode recording; first array
+ 61868	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	with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or receiver
70551	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material
70552	Magnetic resonance (eg, proton) imaging, brain (including brain stem); with contrast material(s)
70553	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material, followed by contrast material(s) and further sequences
95836	Electrocorticogram from an implanted brain neurostimulator pulse generator/transmitter, including recording, with interpretation and written report, up to 30 days
95970	Electronic analysis of implanted neurostimulator pulse generator system (eg, 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 (ie, cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without programming
95971	simple spinal cord, or peripheral (ie, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming

Code	Code Description
95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
95977	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
95983	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/ transmitter programming, first 15 minutes face-to- face time with physician or other qualified health care professional

Code	Code Description
95984	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/ transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)
CPT codes not covered for indications listed in the CPB:	
Placement of fiducials (e.g., WayPoint anchor) –no specific code	
HCPCS codes covered if selection criteria are met:	
C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1787	Patient programmer, neurostimulator
C1816	Receiver and/or transmitter, neurostimulator (implantable)
C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
C1883	Adaptor/ extension, pacing lead or neurostimulator lead (implantable)
C1897	Lead, neurostimulator test kit (implantable)
E0745	Neuromuscular stimulator, electronic shock unit
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension

Code	Code Description
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
L8695	External recharging system for battery (external) for use with implantable neurostimulator, replacement only
ICD-10 codes covered if selection criteria are met:	
G20.A1 – G20.C	Parkinson's disease
G21.0 - G21.9	Secondary Parkinsonism
G24.1	Genetic torsion dystonia
G24.2 - G24.4 G24.8 - G24.9	Other acquired torsion dystonia [intractable primary including generalized and/or segmental, hemidystonia, or cervical - not drug-induced][Not covered for status dystonicus] [Not covered for dystonia due to Anoxic brain injury]
G25.0 - G25.2	Essential and other specified forms of tremor [disabling upper extremity essential] [not covered for orthostatic tremor and post-traumatic tremor]
G40.001 - G40.219	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
A00.0 - B99.9	Infectious and parasitic diseases
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles [focal lesion of basal ganglia, space occupying lesion or lacunae that would negate result]
C79.31	Secondary malignant neoplasm of brain [focal lesion of basal ganglia, space occupying lesion or lacunae that would negate result]
D33.0 - D33.2	Benign neoplasm of brain [focal lesion of basal ganglia, space occupying lesion or lacunae that would negate result]
D43.0 - D43.2 D43.4	Neoplasm of uncertain behavior of brain and spinal cord [focal lesion of basal ganglia, space occupying lesion or lacunae that would negate result]

Code	Code Description
E66.01 - E66.9	Overweight and obesity
E70.0 - E88.9	Metabolic disorders
F02.80 - F02.C4	Dementia in conditions classified elsewhere with or without behavioral disturbance or with behavioral disturbance
F03.90 - F03.C4	Senile and presenile organic psychotic conditions
F10.20 - F10.99	Alcohol related disorders [abuse, dependence, use]
F11.10 - F19.99	Drug related disorders [abuse, dependence, use]
F30.10 - F39	Mood [affective] disorders
F32.81 - F32.89	Other depressive episodes
F34.1	Dysthymic disorder
F42.2 - F42.9	Obsessive-compulsive disorders
F44.4	Conversion disorder with motor symptom or deficit [Parkinson's disease-related camptocormia]
F50.00 - F50.029	Anorexia nervosa
F63.81	Intermittent explosive disorder [explosive aggressive behavior]
F84.0 - F84.9	Pervasive developmental disorders
F95.2	Tourette's disorder
F98.5	Adult onset fluency disorder [Parkinson's diseases-related]
G10	Huntington's chorea
G23.0 - G23.9 G90.3	Other degenerative diseases of the basal ganglia
G24.01	Drug induced subacute dyskinesia
G24.02	Drug induced acute dystonia
G24.5	Blepharospasm
G25.5	Other chorea [chorea-acanthocytosis]
G25.81	Restless legs syndrome

Code	Code Description
G25.9	Extrapyramidal and movement disorder, unspecified [drug-induced]
G30.0 - G30.9	Alzheimer's disease
G35	Multiple sclerosis
G40.301 - G40.89	Epilepsy and recurrent seizures
G44.021 - G44.029	Chronic cluster headaches
G80.0 - G80.9	Cerebral palsy
G81.10 – G81.14	Spastic hemiplegia [Not covered for dystonia due to Anoxic brain injury]
G90.50 - G90.59	Complex regional pain syndrome
G93.1	Anoxic brain damage, not elsewhere classified
H93.11 - H93.19, H93.A1 - H93.A9	Tinnitus
I69.393	Ataxia following cerebral infarction
Q82.0	Meige Syndrome
R22.0 - R22.1 R90.0	Swelling, mass, or lump in head and neck
R25.0 - R25.9	Abnormal involuntary movements
R26.0 - R26.9	Abnormalities of gait and mobility
R29.3	Abnormal posture [postural trunk deformities]
R40.0 - R40.4	Alteration of consciousness
R47.81 - R47.89	Other speech disturbance [Parkinson's diseases-related]
R64	Cachexia [invalidism - Hoehn and Yahr Stage V Parkinson's disease]

Code	Code Description
S04.011S - S04.899S S06.0x0S - S06.9x9S S14.101S - S14.9xxS S24.101S - S24.9xxS S34.101S - S34.9xxS S44.00xS - S44.92xS S54.00xS - S54.92xS S64.00xS - S64.92xS S74.00xS - S74.92xS S84.00xS - S84.92xS S94.00xS - S94.92xS	Injuries to the nervous system, sequela
S06.0x0A - S06.9x9S	Intracranial injury
S66.999S	Other injury of unspecified muscle, fascia and tendon at wrist and hand level of unspecified hand, sequela
X71.0xxA - X83.8xxS	Intentional self-harm
Z74.01	Bed confinement status [invalidism - Hoehn and Yahr Stage V Parkinson's disease]

Background

Essential tremor is a common movement disorder afflicting 5 to 10 million Americans. It is characterized primarily by an action and postural tremor most often affecting the arms, but it can also affect other body parts. Essential tremor is a progressive neurological disorder and can result in severe disability in some individuals. Although there is no cure for essential tremor, pharmacotherapy and surgery can provide some relief. Primidone and propranolol are first-line treatments. Other medications include benzodiazepines, gabapentin, and topiramate. Patients with medication-resistant tremor may benefit from thalamotomy or deep brain stimulation (DBS) of the thalamus. Medical and surgical interventions can provide benefit in up to 80% of patients with essential tremor. Deep brain stimulation is also an effective treatment for patients with advanced Parkinson's disease (PD) and motor complications that can no longer be improved by adjustment of medical therapy. The most common targets for implantation of deep brain stimulators are the subthalamic nucleus and globus pallidus internus.

The American Academy of Neurology's practice parameter on the treatment of PD with motor fluctuations and dyskinesia (Pahwa et al, 2006) stated that pre-operative response to levodopa predicts better outcome after DBS of the subthalamic nucleus.

Deuschl and Bain (2002) noted that the appropriate selection of patients is essential for the outcome of surgical relief of tremors. The selection criteria should include: (i) motor symptoms causing a relevant disability in activities of daily living, despite optimal pharmacotherapy; (ii) biological age of the patient; (iii) neurosurgical contraindications; and (iv) the patient is neither demented nor severely depressed.

Lyons and Pahwa (2008) stated that DBS has been used to treat various tremor disorders for several decades. Medication-resistant, disabling essential tremor is the most common tremor disorder treated with DBS. The treatment has been consistently reported to result in significant benefit in upper extremity, as well as head and voice tremor, all of which were improved more dramatically with bilateral procedures. These benefits have been demonstrated to be sustained for up to 7 years. Deep brain stimualtion has also been shown to be beneficial for the tremor associated with multiple sclerosis and post-traumatic tremor;

however, fewer cases have been reported and the benefit is less consistent, less dramatic, and more transient than that seen with essential tremor. The ventral intermediate nucleus of the thalamus is the most common DBS target for tremor disorders, but more recent studies have demonstrated benefits in tremor from DBS of the subthalamic area, primarily the zona incerta. Surgical complications are relatively uncommon and are generally less frequent than those seen with thalamotomy. Stimulation-related effects are usually mild and resolve with adjustment of stimulation parameters. Deep brain stimulation is thus a relatively safe and effective treatment for tremor disorders, particularly for medication-resistant, disabling essential tremor, but may also have some role in medication-resistant, disabling tremor associated with multiple sclerosis and traumatic head injury.

In a randomized controlled trial (RCT), Weaver and colleagues (2009) compared 6-month outcomes for patients with PD who received DBS (bilateral DBS of the subthalamic nucleus [n = 60] or globus pallidus [n = 61]) or best medical therapy. A total of 255 patients with PD (Hoehn and Yahr stage > or = 2 while not taking medications) were enrolled; 25% were aged 70 years or older. Patients receiving best medical therapy (n = 134) were actively managed by movement disorder neurologists. The primary outcome was time spent in the "on" state (good motor control with unimpeded motor function) without troubling dyskinesia, using motor diaries. Other outcomes included motor function, quality of life, neurocognitive function, and adverse events. Patients who received DBS gained a mean of 4.6 h/d of on time without troubling dyskinesia compared with 0 h/d for patients who received best medical therapy (between group mean difference, 4.5 h/d [95% confidence interval [CI]: 3.7 to 5.4 h/d]; $p < 0.001$). Motor function improved significantly ($p < 0.001$) with DBS versus best medical therapy, such that 71% of DBS patients and 32% of best medical therapy patients experienced clinically meaningful motor function improvements (greater than or equal to 5 points). Compared with the best medical therapy group, the DBS group experienced significant improvements in the summary measure of quality of life and on 7 of 8 PD quality-of-life scores ($p < 0.001$). Neurocognitive testing revealed small decrements in some areas of information processing for patients receiving DBS versus best medical therapy. At least 1 serious adverse event occurred in 49 DBS patients and 15 best medical therapy patients ($p < 0.001$), including 39 adverse events related to the surgical procedure and 1 death secondary to cerebral hemorrhage. The authors

concluded that in this RCT of patients with advanced PD, DBS was more effective than best medical therapy in improving on time without troubling dyskinesias, motor function, and quality of life at 6 months, but was associated with an increased risk of serious adverse events.

An editorial that accompanied the afore-mentioned article, Deuschl (2009) stated that "[t]he cumulative risk for device-related problems was 10% at 6 months, and stimulation-related problems, which mostly can be corrected, were even more frequent .... the suicide rate following deep brain stimulation was 13 times higher in the first postoperative year (24/5,311 patients) and doubled after 4 years .... this study, along with previous research on this therapy, shows that such progress cannot be made without costs in terms of adverse effects".

On the other hand, DBS is an investigational therapy in other conditions such as such as trauma, multiple sclerosis (MS), degenerative disorders, metabolic disorders, infectious diseases, and drug-induced movement disorder. Experience with DBS in the treatment of tremor due to MS is limited to small case series or case reports. Currently, it is impossible to predict which patients will benefit from this treatment. Furthermore, frequent stimulator adjustments are needed to maintain optimum limb functions; and long-term effectiveness has not been demonstrated. Prospective, RCTs with large sample size are needed to ascertain the long-term efficacy of DBS in patients with MS.

The consensus recommendations of the German Deep Brain Stimulation Association on DBS for tremor in MS (Timmermann et al, 2009) noted that the sparse studies on DBS in MS tremor remain controversial regarding the clinical effect on postural and action tremor of hands, trunk and head. Furthermore, it remains unclear if DBS in MS tremor is superior to thalamotomy and if patients show an overall improvement in quality of life and activities of daily living.

In a prospective cohort study, Porta et al (2009) evaluated the long-term outcome on tics, behavioral symptoms, and cognitive functions of thalamic DBS for TS. A total of 15 of the original 18 patients were evaluated before and after surgery according to a standardized protocol that included both neuropsychiatric and neuropsychological assessments. In addition to marked reduction in tic severity ($p = 0.001$), 24-month follow-up ratings showed improvement in obsessive-

compulsive symptoms (p = 0.009), anxiety symptoms (p = 0.001), depressive symptoms (p = 0.001), and subjective perception of social functioning/quality of life (p = 0.002) in 15 of 18 patients. There were no substantial differences on measures of cognitive functions before and after DBS. The authors concluded that at 24-month follow-up, tic severity was improved in patients with intractable TS who underwent bilateral thalamic DBS. Available data from 15 of 18 patients also showed that neuropsychiatric symptoms were improved and cognitive performances were not disadvantaged. Moreover, they stated that controlled studies on larger cohorts with blinded protocols are needed to verify that this procedure is safe and effective for selected patients with TS.

In a 10-month, cross-over, double-blind, multi-center study, Mallet and colleagues (2008) evaluated the safety and effectiveness of stimulation of the subthalamic nucleus in treating OCD. A total of 16 patients with highly refractory OCD were randomly assigned to undergo: (i) active stimulation of the subthalamic nucleus followed by sham stimulation and (ii) sham stimulation followed by active stimulation. The primary outcome measure was the severity of OCD, as assessed by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), at the end of two 3-month periods. General psychopathologic findings, functioning, and tolerance were assessed with the use of standardized psychiatric scales, the Global Assessment of Functioning (GAF) scale, and neuropsychological tests. After active stimulation of the subthalamic nucleus, the Y-BOCS score (on a scale from 0 to 40, with lower scores indicating less severe symptoms) was significantly lower than the score after sham stimulation (mean [+/- SD], 19 +/- 8 versus 28 +/- 7; p = 0.01), and the GAF score (on a scale from 1 to 90, with higher scores indicating higher levels of functioning) was significantly higher (56 +/- 14 versus 43 +/- 8, p = 0.005). The ratings of neuropsychological measures, depression, and anxiety were not modified by stimulation. There were 15 serious adverse events overall, including 1 intra-cerebral hemorrhage and 2 infections; there were also 23 non-serious adverse events. The authors concluded that these preliminary findings suggested that stimulation of the subthalamic nucleus may reduce the symptoms of severe forms of OCD but is associated with a substantial risk of serious adverse events. They noted that the occurrence of severe adverse events, the small number of patients, and the short duration of the study highlight the risks of

stimulation of the subthalamic nucleus and the need for larger studies with longer follow-up.

On February 19, 2009, the Food and Drug Administration (FDA), under a humanitarian device exemption, approved DBS for the treatment of patients with severe OCD who have not responded to conventional therapy (e.g., anti-depressant medications). The approval was based on a review of data from 26 patients with severe treatment-resistant OCD who were treated with the device at 4 sites. On average, patients had a 40 % reduction in their symptoms after 12 months of therapy. While all patients reported adverse events, the majority of these events ended after an adjustment was made in the amount of electrical stimulation. Contraindications for DBS include patients who require electro-convulsive shock therapy, patients who who will undergo magnetic resonance imaging or diathermy.

Although DBS has been approved by the FDA for the treatment of severe OCD, the available evidence is insufficient to support the effectiveness of DBS for this disorder. In a review on OCD, Abramowitz and colleagues (2009) stated that although the initial results of DBS for the treatment of OCD are promising, this intervention should be adequately assessed its safety and effectiveness.

Primary generalized dystonia associated with the early-onset generalized dystonia gene can cause severe disability, affecting a person’s ability to perform activities of daily living. Pharmacotherapy has been inadequate in alleviating the motor dysfunctions. Deep brain stimulation of the bilateral globus pallidus internus has been reported to reduce these debilitating motor abnormalities. The FDA approved DBS for the treatment of primary dystonia via the humanitarian device exemption process, and its summary of safety and probable benefit stated that although there are a number of serious adverse events experienced by patients treated with DBS, 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 dystonia occurs prior to the individual reaching their full adult size, the disease not only can affect normal psychosocial development but also cause irreparable damage to the skeletal system. As the body of the afflicted person 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, except when used in either child or adolescent patients groups.

In this regard, Eltahawy et al (2004) reported that bilateral pallidal stimulation is effective in management of selected cases of intractable cervical dystonia. Furthermore, the findings of a recent prospective, controlled, multicenter study (Vidailhet et al, 2005) support the safety and effectiveness of the use of bilateral stimulation of the internal globus pallidus in selected patients with primary generalized dystonia. However, according to a report by the American Academy of Neurology (Zesiewicz et al, 2005), there is no evidence of a synergistic effect on limb tremor with bilateral DBS, and there are insufficient data regarding the risk:benefit ratios of unilateral versus bilateral DBS. Furthermore, the report also stated that there is insufficient evidence to make recommendations regarding the use of DBS for head or voice tremor.

There is currently insufficient scientific evidence that DBS is effective in treating patients with PD-related dysarthria/speech deficit.

In a review, Schulz and Grant (2000) examined the different treatment approaches for patients with PD and their effects on speech. Therapeutic approaches reviewed include speech therapy, pharmacological, and surgical. The authors stated that research from the 1950s through the 1970s had not shown significant improvements following speech therapy. On the other hand, recent research has shown that speech therapy (when PD patients are optimally medicated) has proven to be most effective in improving voice and speech function. Pharmacotherapies in isolation do not appear to significantly improve voice and speech function in PD patients across research studies. Neurosurgical interventions including pallidotomy and DBS may be significant treatment options which improve voice and speech function in some PD patients. These investigators stated that future studies should examine the effects of combined treatment approaches. Perhaps the combination of pharmacological, neurosurgical, and speech treatment will prove superior to treatments combining pharmacological and neurosurgical approaches, or pharmacotherapies and speech therapy in improving the communication abilities of patients with PD.

Pinto et al (2004) stated that dysarthria in PD can be characterized by monotony of pitch and loudness, reduced stress, variable rate, imprecise consonants, and a breathy and harsh voice. Use of levodopa to replenish dopamine concentrations in the striatum appears to improve articulation, voice quality, and pitch variation, although some studies showed no change in phonatory parameters. Traditional speech therapy can lead to improvement of dysarthria, and intensive programs have had substantial beneficial effects on vocal loudness. Unilateral surgical lesions of subcortical structures are variably effective for the alleviation of dysarthria, whereas bilateral procedures typically lead to worsening of speech production (Pinto et al, 2004). Among DBS procedures, only stimulation of the subthalamic nucleus improves some motor components of speech although intelligibility seems to decrease after surgery. Due to the variable treatment effects on Parkinsonian speech, management of dysarthria is still challenging for the clinician.

Farrell and colleagues (2005) examined the effects of neurosurgical management of PD, including pallidotomy, thalamotomy, and DBS on perceptual speech characteristics, speech intelligibility, and oromotor function in a group of 22 patients with PD. The surgical subjects were compared with a group of 25 non-neurologically impaired individuals matched for age and sex. In addition, the study examined 16 patients with PD who did not undergo neurosurgical treatment to control for disease progression. Results revealed that neurosurgical intervention did not significantly change the surgical subjects' perceptual speech dimensions or oromotor function despite significant post-operative improvements in ratings of general motor function and disease severity.

There is currently insufficient scientific evidence that DBS is effective in treating patients with depression. Eitan and Lerer (2006) stated that non-pharmacological modalities for the treatment of depression such as magnetic seizure therapy, vagus nerve stimulation, and DBS are at various stages of research development. The authors reviewed the development and technical aspects of these treatments, their potential role in the treatment of major depression, adverse effects, and putative mechanism of action. These researchers concluded that although these modalities hold considerable promise, these novel brain stimulation techniques need to be further developed before they achieve clinical acceptability. Carpenter et al (2006) noted that DBS for severe intractable depression has been studied in two pilot studies with

very few patients to date. They stated that further investigations are currently underway in order to more fully evaluate DBS with the hope of substantially improving the treatment of refractory depression. These findings are in agreement with that of (Holtzheimer and Nemeroff, 2006) who stated that for the most part, the data on DBS for the treatment of depression are preliminary, and more study is needed to clarify its potential clinical benefit.

In 2001, the Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT) partnered to produce evidence-based clinical guidelines for the treatment of depressive disorders. These guidelines were revised by CANMAT in 2008 to 2009 to reflect advances in the field (Kennedy et al, 2009). The revised guidelines stated that there is emerging evidence that DBS is effective for otherwise treatment resistant depression, but this approach remains an investigational treatment.

Halpern et al (2008) stated that recent evidence suggested that DBS may be effective and safe in the management of various, refractory neuropsychiatric disorders, including obesity. These researchers reviewed the literature implicating various neural regions in the pathophysiology of obesity, as well as the evidence supporting these regions as targets for DBS, in order to explore the therapeutic promise of DBS in obesity. The lateral hypothalamus and ventromedial hypothalamus are the appetite and satiety centers in the brain, respectively. Substantial data support targeting these regions with DBS for the purpose of appetite suppression and weight loss. However, reward sensation associated with highly caloric food has been implicated in over-consumption as well as obesity, and may in part explain the failure rates of conservative management and bariatric surgery. Thus, regions of the brain's reward circuitry, such as the nucleus accumbens, are promising alternatives for DBS in managing obesity. The authors concluded that DBS should be considered as a promising therapeutic option for patients suffering from refractory obesity.

In a report from the Benign Essential Blepharospasm Research Foundation (BEBRF) International Workshop, Hallett et al (2008) stated that "DBS was recently used to treat patients with disabling cranial dystonia, including blepharospasm, who have become refractory to

other forms of therapy .... Very few patients have been studied so far, but given the clear utility of DBS for dystonia, further studies for blepharospasm will certainly be undertaken".

Lyons et al (2010) stated that Meige syndrome is characterized by blepharospasm, cervical dystonia, and facial oromandibular dystonia. The medical treatment of this condition is largely unsuccessful over time and is a major source of decreased quality of life in those patients suffering from this disease. Recent advances in the application of DBS surgery techniques for many disorders have prompted several recent reports of DBS for medically refractory cases of Meige syndrome. While the etiology for this disorder is unknown, it is considered by many investigators to be a form of idiopathic torsion dystonia. Pallidal stimulation is widely considered to be effective for dystonia. These researchers reported the long-term results of bilateral globus pallidus internus (GPi) or subthalamic nucleus (STN) stimulation in 3 patients with Meige syndrome and 1 patient with PD and associated craniofacial dystonia treated at their center. Initial 12-month and long-term follow-up Burke-Fahn-Marsden scores were substantially improved in all 4 patients compared with pre-operative scores. The authors concluded that bilateral GPi DBS may be an effective and safe treatment for medically refractory Meige syndrome. The results are comparable with those reported in the literature. Sustained and long-term improvement in symptoms does appear to be reproducible across reports. The authors' patient with PD and associated craniofacial dystonia syndrome undergoing bilateral STN DBS noted immediate and sustained improvement in his symptoms. They stated that further study is required, but these results, along with the other reports, suggest that bilateral GPi DBS is an effective treatment for medically refractory Meige syndrome.

Georgiopoulos et al (2010) performed a systematic review of the proposed medical or surgical treatments in patients in chronic vegetative state (CVS) or minimally conscious state (MCS), as well as of their mechanisms of action and limitations. These investigators included patients in CVS or MCS having persisted for over 6 months in post-traumatic cases, and over 3 months in non-traumatic cases, before the time of intervention. Searches were independently conducted by 2 investigators between May 2009 and September 2009 in the following databases: Medline, Web of Science and the Cochrane Library. The electronic search was complemented by cross-checking

the references of all relevant articles. Overall, 16 papers were eligible for this systematic review. According to the 16 eligible studies, medical management by dopaminergic agents (levodopa, amantadine), zolpidem and median nerve stimulation, or surgical management by DBS, extradural cortical stimulation, spinal cord stimulation and intrathecal baclofen have shown to improve the level of consciousness in certain cases. The authors concluded that treatments proposed for disorders of consciousness have not yet gained the level of "evidence-based treatments"; moreover, the studies to date have led to inconclusiveness. The published therapeutic responses must be substantiated by further clinical studies of sound methodology.

Authors of an article in Health Affairs (Fins et al, 2011) argued that the humanitarian device exemption (HDE) for DBS for OCD should be rescinded since there is little evidence to support its safe and effective use. Fins et al (2011) stated that DBS is emerging as a treatment of last resort for people diagnosed with neuropsychiatric disorders such as severe OCD. The FDA granted HDE to allow patients to access this intervention, thereby removing the requirement for a clinical trial of the appropriate size and statistical power. Bypassing the rigors of such trials puts patients at risk, limits opportunities for scientific discovery, and gives device manufacturers unique marketing opportunities. The authors argued that Congress and federal regulators should re-visit the HDE to ensure that it is not used to side-step careful research that can offer valuable data with appropriate patient safeguards.

Muller et al (2011) developed a European guideline on DBS by a working group of the European Society for the Study of Tourette Syndrome (ESSTS). For a narrative review, a systematic literature search was conducted and expert opinions of the guidelines group contributed also to the suggestions. Of 63 patients reported so far in the literature, 59 had a beneficial outcome following DBS with moderate to marked tic improvement. However, randomized controlled studies including a larger number of patients are still lacking. Although persistent serious adverse effects (AEs) have hardly been reported, surgery-related (e.g., bleeding, infection) as well as stimulation-related AEs (e.g., sedation, anxiety, altered mood, changes in sexual function) may occur. At present time, DBS in TS is still in its infancy. Due to both different legality and practical facilities in different European countries these guidelines, therefore, have to be understood as recommendations of experts. However, among the ESSTS working

group on DBS in TS there is general agreement that, at present time, DBS should only be used in adult, treatment resistant, and severely affected patients. It is highly recommended to perform DBS in the context of controlled trials.

Kang et al (2011) noted that DBS has been shown to be effective in the treatment of various movement disorders including PD, essential tremor and dystonia. However, there is limited information regarding the potential use of DBS in Huntington's disease (HD). In this study, the authors presented their findings on the long-term motor and neurocognitive results of 2 HD patients (patient 1: 57 years, 42 cytosine-adenine guanine (CAG) repeats; patient 2: 50 years, 41 CAG repeats) who underwent staged bilateral globus pallidus interna DBS surgery. The patients were evaluated at baseline and at 5 time points throughout a 2-year post-operative during which motoric ratings ((Unified Huntington's Disease Rating Scale), Activities of Daily Living scores (HD-ADL) and neurocognitive testing) were obtained. Both patients had a sustained decline in chorea 2 and 14 years after initial DBS surgery. Despite this improvement in chorea, 1 patient has had continuing deterioration in gait, bradykinesia and dystonia scores, which has caused his ability to perform activities of daily living to return to his baseline level of functioning prior to DBS surgery. Both patients have experienced further gradual decline in neurocognitive functioning, which appears to be independent of DBS and most likely related to disease progression. The authors concluded that DBS implantation may be a potential treatment option for a subset of HD patients who have significant functional deficits due to chorea. However, appropriate selection of the best candidates for DBS appears to be challenging, given the difficulty in predicting disease course in HD due to its variable nature.

Halpern et al (2011) noted that the indications for DBS are expanding, and the feasibility and efficacy of this surgical procedure in various neurologic and neuropsychiatric disorders continue to be tested. This review attempts to provide background and rationale for applying this therapeutic option to obesity and addiction. These researchers reviewed neural targets currently under clinical investigation for DBS -- the hypothalamus and nucleus accumbens -- in conditions such as cluster headache and OCD. These brain regions have also been strongly implicated in obesity and addiction. These disorders are frequently refractory, with very high rates of weight regain or relapse,

respectively, despite the best available treatments. These investigators performed a structured literature review of the animal studies of DBS, which revealed attenuation of food intake, increased metabolism, or decreased drug seeking. They also reviewed the available radiologic evidence in humans, implicating the hypothalamus and nucleus in obesity and addiction. The available evidence of the promise of DBS in these conditions combined with significant medical need, support pursuing pilot studies and clinical trials of DBS in order to decrease the risk of dietary and drug relapse. The authors concluded that well-designed pilot studies and clinical trials enrolling carefully selected patients with obesity or addiction should be initiated.

Luigjes et al (2012) stated that DBS is currently investigated in psychiatry for the treatment of refractory OCD, Tourette syndrome and depressive disorder. Although recent research in both animals and humans has indicated that DBS may be an effective intervention for patients with treatment-refractory addiction, it is not yet entirely clear which brain areas should be targeted. The objective of this review was to provide a systematic overview of the published literature on DBS and addiction and outline the most promising target areas using efficacy and adverse event data from both preclinical and clinical studies. These researchers found 7 animal studies targeting 6 different brain areas: (i) nucleus accumbens (NAc), (ii) subthalamic nucleus (STN), (iii) dorsal striatum, (iv) lateral habenula, (v) medial prefrontal cortex (mPFC) and (vi) hypothalamus, and 11 human studies targeting 2 different target areas: (i) NAc and (ii) STN. The analysis of the literature suggests that the NAc is currently the most promising DBS target area for patients with treatment-refractory addiction. The mPFC is another promising target, but needs further exploration to establish its suitability for clinical purposes. The authors concluded the review with a discussion on translational issues in DBS research, medical ethical considerations and recommendations for clinical trials with DBS in patients with addiction.

Bronte-Stewart (2012) stated that high-frequency DBS is an established therapy for PD, essential tremor, and primary dystonia, and is under investigation for several neuropsychiatric diseases. Peri-operative risks include hemorrhage and stroke (less than 2%) and infection (approximately 8%). The benefit/risk ratio may be optimized with individualized patient selection and the use of an experienced surgical team. Bilateral ablations pose an unacceptable risk of speech

impairment and disequilibrium. In a review on “Major depressive disorder: New clinical, neurobiological, and treatment perspectives”, Kupfer et al (2012) noted that DBS is a promising treatment for treatment-resistant depression.

Cruccu et al (2007) stated that pharmacological relief of neuropathic pain is often insufficient. Electrical neurostimulation is efficacious in chronic neuropathic pain and other neurological diseases. European Federation of Neurological Societies (EFNS) launched a Task Force to evaluate the evidence for these techniques and to produce relevant recommendations. These investigators searched the literature from 1968 to 2006, looking for neurostimulation in neuropathic pain conditions, and classified the trials according to the EFNS scheme of evidence for therapeutic interventions. Spinal cord stimulation (SCS) is efficacious in failed back surgery syndrome and complex regional pain syndrome (CRPS) type I (level B recommendation). High-frequency transcutaneous electrical nerve stimulation (TENS) may be better than placebo (level C) although worse than electro-acupuncture (level B). One kind of repetitive transcranial magnetic stimulation (rTMS) has transient efficacy in central and peripheral neuropathic pains (level B). Motor cortex stimulation (MCS) is efficacious in central post-stroke and facial pain (level C). Deep brain stimulation (DBS) should only be performed in experienced centers. Evidence for implanted peripheral stimulations is inadequate. TENS and r-TMS are non-invasive and suitable as preliminary or add-on therapies. The authors concluded that further controlled trials are warranted for SCS in conditions other than failed back surgery syndrome and CRPS and for MCS and DBS in general. These chronically implanted techniques provide satisfactory pain relief in many patients, including those resistant to medication or other means.

The Washington State Department of Labor and Industries' clinical practice guideline on "Work-related complex regional pain syndrome (CRPS): Diagnosis and treatment" (2011) did not mention the use of DBS as a therapeutic option. Furthermore, UpToDate reviews on "Prevention and management of complex regional pain syndrome in adults" (Abdi, 2012) and "Complex regional pain syndrome in children" (Sherry, 2012) do not mention the use of DBS as a therapeutic option.

Plow et al (2012) noted that chronic neuropathic pain is one of the most prevalent and debilitating disorders. Conventional medical management, however, remains frustrating for both patients and clinicians owing to poor specificity of pharmacotherapy, delayed onset of analgesia and extensive side effects. Neuromodulation presents as a promising alternative, or at least an adjunct, as it is more specific in inducing analgesia without associated risks of pharmacotherapy. These investigators discussed common clinical and investigational methods of neuromodulation. Compared to clinical SCS, investigational techniques of cerebral neuromodulation, both invasive (DBS and MCS) and non-invasive (rTMS and transcranial direct current stimulation), may be more advantageous. By adaptively targeting the multi-dimensional experience of pain, subtended by integrative pain circuitry in the brain, including somatosensory and thalamocortical, limbic and cognitive, cerebral methods may modulate the sensory-discriminative, affective-emotional and evaluative-cognitive spheres of the pain neuromatrix. Despite promise, the current state of results alludes to the possibility that cerebral neuromodulation has thus far not been effective in producing analgesia as intended in patients with chronic pain disorders. These techniques, thus, remain investigational and off-label. These researchers discussed issues implicated in inadequate efficacy, variability of responsiveness, and poor retention of benefit, while recommending design and conceptual refinements for future trials of cerebral neuromodulation in management of chronic neuropathic pain.

Marks and colleagues (2012) noted that cerebral palsy (CP) is the most common cause of pediatric-onset dystonia. Deep brain stimulation is gaining acceptance for treating dystonias in children. There is minimal reported experience regarding the effectiveness of DBS in CP. A total of 14 patients, including 8 younger than 16 years, received bilateral implants (13 patients) or a unilateral implant (1 patient) of the internal globus pallidus and were observed in a non-controlled, non-blinded study for at least 6 months. Motor function was assessed using the Burke-Fahn-Marsden Dystonia Movement and Disability scales and the Barry Albright Dystonia Scale. By 6 months, significant improvement was observed in the Burke-Fahn-Marsden Dystonia Movement scale ($p = 0.004$), the Burke-Fahn-Marsden Dystonia Disability scale ($p = 0.027$), and the Barry Albright Dystonia Scale ($p = 0.029$) for the whole cohort ($n = 14$) and in the patients treated before skeletal maturity (group 1; $n = 8$): Burke-Fahn-Marsden Dystonia Movement scale, $p = 0.012$; Burke-Fahn-Marsden Dystonia Disability scale, $p = 0.020$; and

Barry Albright Dystonia Scale, p = 0.027. The authors concluded that DBS may offer an effective treatment option for CP-related dystonia, especially in those treated before skeletal maturity. The findings of this small, non-controlled, and non-blinded study need to be validated by well-designed studies.

Koy et al (2013) stated that secondary dystonia encompasses a heterogeneous group with different etiologies. Cerebral palsy is the most common cause. Pharmacological treatment is often unsatisfactory. There are only limited data on the therapeutic outcomes of DBS in dyskinetic CP. The published literature regarding DBS and secondary dystonia was reviewed in a meta-analysis to re-evaluate the effect on CP. The Burke-Fahn-Marsden Dystonia Rating Scale movement score was chosen as the primary outcome measure. Outcome over time was evaluated and summarized by mixed-model repeated-measures analysis, paired Student t-test, and Pearson's correlation coefficient. A total of 20 articles comprising 68 patients with CP undergoing DBS 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 pre-operatively and dropped to 50.5 ± 26.77 post-operatively, with a mean improvement of 23.6% ($p < 0.001$) at a median follow-up of 12 months. The mean Burke-Fahn-Marsden Dystonia Rating Scale disability score was 18.54 ± 6.15 pre-operatively and 16.83 ± 6.42 post-operatively, with a mean improvement of 9.2% ($p < 0.001$). There was a significant negative correlation between severity of dystonia and clinical outcome ($p < 0.05$). The authors concluded that DBS can be an effective treatment option for dyskinetic CP. Moreover, they stated that i view of the heterogeneous data, a prospective study with a large cohort of patients in a standardized setting with a multi-disciplinary approach would be helpful in further evaluating the role of DBS in CP.

In a pilot study, Lipsman et al (2013) evaluated the safety of DBS to modulate the activity of limbic circuits and examined how this might affect the clinical features of anorexia nervosa (AN). These researchers performed a phase I, prospective trial of subcallosal cingulate DBS in 6 patients with chronic, severe, and treatment-refractory AN. Eligible patients were aged 20 to 60 years, had been diagnosed with restricting or binge-purging AN, and showed evidence of chronicity or treatment

resistance. Patients underwent medical optimization pre-operatively and had baseline body-mass index (BMI), psychometric, and neuroimaging investigations, followed by implantation of electrodes and pulse generators for continuous delivery of electrical stimulation. Patients were followed-up for 9 months after DBS activation, and the primary outcome of adverse events associated with surgery or stimulation was monitored at every follow-up visit. Repeat psychometric assessments, BMI measurements, and neuroimaging investigations were also done at various intervals. Deep brain stimulation was associated with several adverse events, only one of which (seizure during programming, roughly 2 weeks after surgery) was serious. Other related adverse events were panic attack during surgery, nausea, air embolus, and pain. After 9 months, 3 of the 6 patients had achieved and maintained a BMI greater than their historical baselines. Deep brain stimulation was associated with improvements in mood, anxiety, affective regulation, and AN-related obsessions and compulsions in 4 patients and with improvements in quality of life in 3 patients after 6 months of stimulation. These clinical benefits were accompanied by changes in cerebral glucose metabolism (seen in a comparison of composite PET scans at baseline and 6 months) that were consistent with a reversal of the abnormalities seen in the anterior cingulate, insula, and parietal lobe in the disorder. The authors concluded that subcallosal cingulate DBS seems to be generally safe in this sample of patients with chronic and treatment-refractory AN. The effectiveness of DBS in the treatment of patients with AN needs to be validated by well-designed studies.

Wu and colleagues (2013) stated that AN is a complex and severe, sometimes life-threatening, psychiatric disorder with high relapse rates under standard treatment. After decades of brain-lesioning procedures offered as a last resort, DBS has come under investigation in the last few years as a treatment option for severe and refractory AN. In this jointly written article, Sun et al (the Shanghai group) reported an average of 65% increase in body weight in 4 severe and refractory patients with AN after they underwent the DBS procedure (average follow-up of 38 months). All patients weighed greater than 85% of expected body weight and thus no longer met the diagnostic criteria of AN at last follow-up. Nuttin et al (the Leuven group) described other clinical studies that provided evidence for the use of DBS for AN; and further discussed patient selection criteria, target selection, and adverse event of this evolving therapy. The authors concluded that

preliminary results from the Shanghai group and other clinical centers showed that the use of DBS to treat AN may be a valuable option for weight restoration in otherwise-refractory and life-threatening cases. The nature of this procedure, however, remains investigational and should not be viewed as a standard clinical treatment option. They stated that further scientific investigation is essential to determine the long-term and safety and effectiveness of DBS for AN.

Lemaire et al (2014) reported that 6 clinical studies of chronic electrical modulation of deep brain circuits published between 1968 and 2010 have reported effects in 55 vegetative or minimally conscious patients. The rationale stimulation was to activate the cortex through the reticular-thalamic complex, comprising the tegmental ascending reticular activating system and its thalamic targets. The most frequent intended target was the central intralaminar zone and adjacent nuclei. Hassler et al also proposed to modulate the pallidum as part of the arousal and wakefulness system. Stimulation frequency varied from 8 Hz to 250 Hz. Most patients improved, although in a limited way. Schiff et al found correlations between central thalamus stimulation and arousal and conscious behaviors. Other treatments that have offered some clinical benefit include drugs, repetitive magnetic transcranial stimulation, median nerve stimulation, stimulation of dorsal column of the upper cervical spinal cord, and stimulation of the fronto-parietal cortex. No one treatment has emerged as a gold standard for practice, which is why clinical trials are still on-going. The authors concluded that further clinical studies are needed to decipher the altered dynamics of neuronal network circuits in patients suffering from severe disorders of consciousness as a step towards novel therapeutic strategies.

Bartsch and Kuhn (2014) reviewed the current state of DBS in the treatment of refractory OCD. In addition, initial experimental approaches to investigate the potential use of DBS in substance addiction and AN were outlined as both disorders share some common features with OCD. The present review was based on a keyword literature search (PubMed) while taking into account relevant references and own investigations. Although the number of clinical trials for treatment of refractory OCD is limited and sample sizes are small, there is some evidence for a substantial improvement, a so-called full response of OCD symptoms under DBS. However, not all patients benefit from the intervention. Regarding substance addiction

and AN, data are scarce and are only indicative of a potential benefit at most. The authors concluded that present data regarding the clinical benefits of DBS in OCD are encouraging and open up new avenues for the treatment of therapy refractory patients. However, several aspects, such as mechanisms of action, predictors and long-term side effect profiles, are incomplete or even unknown. In the case of addiction and AN, DBS remains purely experimental, at least for the moment. Hence, clinical trials should remain the gold standard for all three indications.

Kohl et al (2014) noted that OCD is one of the most disabling of all psychiatric illnesses. Despite available pharmacological and psychotherapeutic treatments about 10% of patients remain severely affected and are considered treatment-refractory. For some of these patients DBS offers an appropriate treatment method. These researchers reviewed the published data and compared different target structures and their effectiveness. PubMed search, last update June 2013, was conducted using the terms "deep brain stimulation" and "obsessive compulsive disorder". A total of 25 studies were found that reported 5 DBS target structures to treat OCD: (i) the anterior limb of the internal capsule (5 studies including 14 patients), (ii) nucleus accumbens (8 studies including 37 patients), (iii) ventral capsule/ventral striatum (4 studies including 29 patients), (iv) subthalamic nucleus (5 studies including 23 patients) and (v) inferior thalamic peduncle (2 studies including 6 patients). Despite the anatomical diversity, DBS treatment results in similar response rates for the first four target structures. Inferior thalamic peduncle DBS results in higher response rates but these results have to be interpreted with caution due to a very small number of cases. Procedure and device related adverse events are relatively low, as well as stimulation or therapy related side effects. Most stimulation related side effects are transient and decline after stimulation parameters have been changed. The authors concluded that DBS in treatment-refractory OCD seems to be a relatively safe and promising treatment option. However, based on these studies no superior target structure could be identified. They stated that more research is needed to better understand mechanisms of action and response predictors that may help to develop a more personalized approach for these severely affected OCD patients.

Kisely et al (2014) performed a systematic review and meta-analysis of the effectiveness of DBS in psychiatric conditions (including OCD) to maximize study power. These researchers conducted a systematic literature search for double-blind, RCTs of active versus sham treatment using PubMed/Medline and EMBASE up to April 2013. Where possible, they combined results from studies in a meta-analysis. They assessed differences in final values between the active and sham treatments for parallel-group studies and compared changes from baseline score for cross-over designs. Inclusion criteria were met by 5 studies, all of which were of OCD. A total of 44 subjects provided data for the meta-analysis. The main outcome was a reduction in obsessive symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS). Patients on active, as opposed to sham, treatment had a significantly lower mean score [mean difference (MD) -8.93, 95% CI: -13.35 to -5.76, $p < 0.001$], representing partial remission. However, 1/3 of patients experienced significant adverse effects (n = 16). There were no differences between the two groups in terms of other outcomes. The authors concluded that DBS may show promise for treatment-resistant OCD but there are insufficient randomized controlled data for other psychiatric conditions. They stated that DBS remains an experimental treatment in adults for severe, medically refractory conditions until further data are available.

Berlim et al (2014) stated that DBS applied to the subgenual cingulate cortex (SCC) has been recently investigated as a potential treatment for severe and chronic treatment-resistant depression (TRD). Given its invasive and experimental nature, a comprehensive evaluation of its effectiveness and acceptability is of paramount importance. These investigators conducted a systematic review and exploratory meta-analysis. They searched the literature for English language prospective clinical trials on DBS of the SCC for TRD from 1999 through December 2012 using MEDLINE, EMBASE, PsycINFO, CENTRAL and SCOPUS, and performed a random effects exploratory meta-analysis using Event Rates and Hedges′ g effect sizes. Data from 4 observational studies were included, totaling 66 subjects with severe and chronic TRD. Twelve-month response and remission rates following DBS treatment were 39.9% (95% CI: 28.4% to 52.8%) and 26.3% (95% CI: 13% to 45.9%), respectively. Also, depression scores at 12 months post-DBS were significantly reduced (i.e., pooled Hedges′ g effect size=-1.89 [95% CI: -2.64 to -1.15, $p < 0.0001$]). Also, there was a significant decrease in depression scores between 3 and 6 months (Hedges′ g =

-0.27, p = 0.003), but no significant changes from months 6 to 12. Finally, dropout rates at 12 months were 10.8% (95% CI: 4.3% to 24.4%). The authors concluded that DBS applied to the SCC seems to be associated with relatively large response and remission rates in the short- and medium- to long-term in patients with severe TRD. Also, its maximal anti-depressant effects are mostly observed within the first 6 months after device implantation. Nevertheless, these findings are clearly preliminary and future controlled trials should include larger and more representative samples, and focus on the identification of optimal neuroanatomical sites and stimulation parameters. The drawbacks of this meta-analysis included small number of included studies (most of which were open label), and limited long-term effectiveness data.

Parkinson's Disease-Related Camptocormia

Schulz-Schaeffer and colleagues (2015) stated that although some reports on neurostimulation are positive, no effective treatment method for camptocormia in PD is known to-date. These researchers identified prognostic factors for a beneficial DBS effect on camptocormia. In an observational cohort study, the authors investigated 25 idiopathic PD patients, who suffered additionally from camptocormia, and underwent bilateral neurostimulation of the STN to improve classical PD symptoms. A beneficial neurostimulation effect on camptocormia was defined as an improvement in the bending angle of a least 50%. In 13 patients, the bending angle of camptocormia improved, in 12 patients it did not. A multi-factorial analysis revealed a short duration between onset of camptocormia and start of neurostimulation to be the relevant factor for outcome. All patients with duration of camptocormia up to 1.5 years showed a beneficial effect; patients between 1.5 and approximately 3 years showed mixed results, but none with a duration of more than 40 months improved except for 1 patient whose camptocormia was levodopa-responsive. The bending angle was not a prognostic factor. These findings indicated that the main prognostic factor for a beneficial DBS effect on camptocormia is its short duration. The authors suggested that neurostimulation may improve camptocormia only as long as muscle pathology is limited. They stated that their findings may help to elucidate the mode of action of neurostimulation; a prospective study is needed.

In a systematic review, Chieng et al (2015) profiled the various reported interventions for camptocormia in PD and gave an overview of the benefits of DBS. Currently, there is no consensus in the literature

regarding this. Parkinson's disease manifests in several ways and camptocormia is one of the commonly encountered problems for both spine and functional neurosurgeons. It is a significant forward flexion of the thoraco-lumbar spine that resolves in the recumbent position. These investigators reviewed the PubMed and Medical Subject Headings database using the phrases "Parkinson's disease" or "Parkinson" in combination with "spinal deformity" or "camptocormia" or "bent spine syndrome" and "deep brain stimulation". The review was limited to English language literature and these researchers excluded camptocormia of non-PD origin. The search yielded 361 articles with 131 patients in the pooled data. The majority (59%) of patients were women and the age range was 48 to 76 years. While 50% of the patients on levodopa (n = 42) saw no improvement of their camptocormia, 71% of the lidocaine group (n = 27) and 68% of the DBS group (n = 32) showed significant improvement. For mean flexion angle, the spinal surgery and DBS group demonstrated profound improvement in the bending angle, 89.9% and 78.2%, respectively. However, major complications following spinal surgery were noted. The authors concluded that although the results were from a small group of patients, DBS has achieved sustained improvement in camptocormia with low post-operative morbidity, and appeared to be a promising treatment option. Moreover, they stated that a larger, long-term study is needed to establish comprehensive outcome data.

Postural Instability and Gait Disorder in Parkinson Disease

Golestanirad and associates (2016) stated that pedunculo-pontine nucleus (PPN) has complex reciprocal connections with basal ganglia, especially with internal globus pallidus and substantia nigra, and it has been postulated that PPN stimulation may improve gait instability and freezing of gait. In this meta-analysis, these investigators evaluated the evidence for PPN-DBS in treatment of gait and motor abnormalities especially focusing on PD patients. PubMed and Scopus electronic databases were searched for related studies published before February 2014. Medline (1966 to 2014), Embase (1974 to 2010), CINAHL, Web of Science, Scopus bibliographic, and Google Scholar databases (1960 to 2014) were also searched for studies investigating effect of PPN-DBS in treatment of postural and postural instability; and a total of 10 studies met the inclusion criteria for this analysis. The results showed a significant improvement in postural instability ($p < 0.001$) and motor symptoms of PD on and off medications ($p < 0.05$), but failed to show improvement in freezing of gait. The authors

concluded that despite significant improvement in postural instability observed in included studies, evidence from current literature is insufficient to generalize these findings to the majority of patients.

Wang and colleagues (2017) noted that postural instability and gait disorder (PIGD) in PD has been a great challenge in clinical practice because PIGD is closely linked to major morbidity and mortality in PD; and PPN has been considered as a potential promising target for DBS in the treatment of PIGD. These researchers performed a meta-analysis of individual patient data to assess the effects of PPN-DBS on PIGD in patients with PD and explored the factors predicting good outcome. According to the study strategy, these investigators searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials, and other sources. After searching the literature, 2 investigators independently screened the literature, assessed the quality of the included trials, and extracted the data. The outcome measures included PIGD, freezing of gait, and falling in PD. Then, individual patient data were incorporated into SPSS software for statistical analyses across series. A total of 6 studies reporting individual patient data were included for final analysis; PPN-DBS significantly improved PIGD as well as freezing of gait and falling after PD, which was depending on the duration of follow-up and types of outcome measures. In addition, patient age, disease duration, levodopa-equivalent dosage, and the choice of unilateral or bilateral stimulation were similar in groups of patients with PD with or without improvement in PIGD after PPN-DBS. The authors concluded that the findings of this study provided evidence that PPN-DBS may improve PIGD, which should be interpreted with caution; and that these results need further verification before generalization of these findings can be made.

Depression

Mayberg et al (2005) stated that treatment-resistant depression (TRD) is a severely disabling disorder with no proven therapeutic options once multiple medications, psychotherapy, and electro-convulsive therapy (ECT) have failed. Based on their preliminary observation that the subgenual cingulate (SGC) region (Brodmann area 25) is metabolically overactive in TRD, these researchers examined if the application of chronic deep brain stimulation (DBS) to modulate BA25 could reduce this elevated activity and produce clinical benefit in 6 patients with refractory depression. Chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with a

striking and sustained remission of depression in 4 of 6 patients. Anti-depressant effects were associated with a marked reduction in local cerebral blood flow (CBF) as well as changes in down-stream limbic and cortical sites, measured using positron emission tomography (PET). The authors concluded that these findings suggested that disrupting focal pathological activity in limbic-cortical circuits using electrical stimulation of the subgenual cingulate white matter could effectively reverse symptoms in otherwise TRD.

These researchers stated that despite these encouraging results, there were drawbacks to this first study of Cg25WM DBS for TRD. Sample size was small (n = 6), follow-up was limited, and no sham surgery or systematic placebo control arm was used. There was also inadequate power to identify demographic, clinical, subtype, neuropsychological, or imaging markers that might predict response. It may be relevant that all 4 responders had their 1st major depressive episode (MDE) before age 35 years and had predominant melancholic features whereas the 2 non-responders had 1st episodes in their 40s and had more atypical symptoms. Differences in electrode targeting and placement and stimulation parameters may have also contributed to the observed response variance. The relative contribution of these various factors will require testing of additional subjects. In the future, the possible interactions between DBS and anti-depressant medications need to be examined.

Lozano et al (2008) noted that a preliminary report in 6 patients suggested that DBS of the SCG may provide benefit in TRD. These researchers reported the results of these and an additional 14 patients with extended follow-up. A total of 20 patients with TRD underwent serial assessments before and after SCG DBS. These investigators determined the percentage of patients who achieved a response (50 % or greater reduction in the 17-item Hamilton Rating Scale for Depression [HRSD-17]) or remission (scores of 7 or less) after surgery. They also examined changes in brain metabolism associated with DBS, using positron emission tomography (PET). There were both early and progressive benefits to DBS. One month after surgery, 35 % of patients met criteria for response with 10 % of patients in remission. Six months after surgery, 60 % of patients were responders and 35 % met criteria for remission, benefits that were largely maintained at 12 months; DBS therapy was associated with specific changes in the metabolic activity localized to cortical and limbic circuits

implicated in the pathogenesis of depression. The number of serious adverse effects was small with no patient experiencing permanent deficits. The authors concluded that the findings of this study suggested that DBS was relatively safe and provided significant improvement in patients with TRD. Subcallosal cingulate gyrus DBS likely acted by modulating brain networks whose dysfunction leads to depression. The procedure was well-tolerated and benefits were sustained for at least 1 year. These researchers stated that while these results, particularly in this difficult-to-treat population, were promising, they represented an initial step and a double- blinded evaluation of DBS in TRD is needed before it could be adopted on a wider scale.

Kennedy et al (2011) noted that a prevalence of at least 30 % for TRD has prompted the investigation of alternative treatment strategies; DBS is a promising targeted approach involving the bilateral placement of electrodes at specific neuroanatomical sites. Given the invasive and experimental nature of DBS for TRD, it is important to obtain both short-term and long-term safety and effectiveness data. In an open-label study, these investigators reported an extended follow-up of 20 patients with TRD who received DBS to the SCG (Brodmann's area 25). After an initial 12-month study of DBS, patients were examined annually and at a last follow-up visit to evaluate depression severity, functional outcomes, and AEs. The average response rates 1, 2, and 3 years after DBS implantation were 62.5 %, 46.2 %, and 75 %, respectively. At the last follow-up visit (range of 3 to 6 years), the average response rate was 64.3 %. Functional impairment in the areas of physical health and social functioning progressively improved up to the last follow-up visit. No significant AEs were reported during this follow-up, although 2 patients died by suicide during depressive relapses. The authors concluded that these data suggested that in the long-term, DBS remained a safe and effective treatment for TRD; however, additional trials with larger samples are needed to confirm these findings. Moreover, these researchers stated that the death of 2 patients by suspected suicide suggested use of caution and reinforced the need for long-term psychiatric management, including psychosocial and pharmacologic therapies, in combination with DBS.

The authors stated that this study had several drawbacks. First, it was an open-label trial, which limited their ability to draw conclusions regarding the effectiveness of DBS. Although it was possible that the symptom improvements observed were due to placebo effects or the

non-specific aspects of psychiatric care, sustained anti-depressant response for longer than 3 years in a cohort of patients with TRD was inconsistent with a placebo response, especially when battery failure was associated with return of symptoms. However, there was a need for double-blind, sham-controlled studies to examine if DBS is an effective anti-depressant therapy. Second, the subjects in this study suffered from non-psychotic unipolar major depression, and it was unclear if these results would be generalizable to patients with other subtypes of major depression or bipolar disorder. Third, only clinical assessments were performed during the long-term follow-up of these patients. The lack of biological data and the small sample size (n = 20) limited analyses of biological mediators and moderators.

Holtzheimer et al (2012) noted that DBS may be an effective intervention for TRD, but available data are limited. In an open-label trial with a sham lead-in phase, these researchers examined the safety and effectiveness of subcallosal cingulate (SCC) DBS in patients with TRD with either major depressive disorder (MDD) or bipolar II disorder (BP). Subjects were men and women aged 18 to 70 years with a moderate-to-severe major depressive episode after at least 4 adequate anti-depressant treatments. A total of 10 patients with MDD and 7 with BP were enrolled from a total of 323 patients screened. Deep brain stimulation electrodes were implanted bilaterally in the subcallosal cingulate white matter. Patients received single-blind sham stimulation for 4 weeks followed by active stimulation for 24 weeks. Patients then entered a single-blind discontinuation phase; this phase was stopped after the first 3 patients because of ethical concerns. Patients were evaluated for up to 2 years after the onset of active stimulation. Change in depression severity and functioning over time, and response and remission rates after 24 weeks were the primary efficacy endpoints; secondary efficacy endpoints were 1 year and 2 years of active stimulation. A significant decrease in depression and increase in function were associated with chronic stimulation. Remission and response were observed in 3 patients (18 %) and 7 (41 %) after 24 weeks (n = 17), 5 (36 %) and 5 (36 %) after 1 year (n = 14), and 7 (58 %) and 11 (92 %) after 2 years (n = 12) of active stimulation. No patient achieving remission experienced a spontaneous relapse. Efficacy was similar for patients with MDD and those with BP. Chronic DBS was safe and well-tolerated, and no hypomanic or manic episodes occurred. A modest sham stimulation effect was found, likely due to a decrease in depression after the surgical intervention but prior to

entering the sham phase. The authors concluded that the findings of this study supported the long-term safety and anti-depressant efficacy of subcallosal cingulate DBS for TRD and suggested equivalent safety and efficacy for TRD in patients with BP. These researchers stated that the next steps in developing this intervention included double-blind trials with a longer sham stimulation period, careful attention to potential demographic and clinical predictors of response and remission, and efforts aimed at decreasing time to remission, such as adjunctive psychotherapeutic rehabilitation.

The authors stated that the main drawbacks of this study included small sample size (n = 10 for the TRD group) and the limited duration and single-blind design of the sham control periods. Furthermore, if the blinded discontinuation phase had occurred in all patients, a stronger statement could be made about the efficacy of active versus sham stimulation. Finally, this study was designed to examine the preliminary safety of SCC DBS in patients with BP, given reports of manic symptoms with DBS of other targets. Therefore, this study was powered to find only large differences in efficacy between the MDD and BP group; a larger trial would be needed to identify small-to-moderate differences in effectiveness.

Riva-Posse et al (2014) SCC DBS is an evolving investigational treatment for depression. Mechanisms of action are hypothesized to involve modulation of activity within a structurally defined network of brain regions involved in mood regulation. Diffusion tensor imaging was used to model white matter connections within this network to identify those critical for successful anti-depressant response. In this study, pre-operative high-resolution magnetic resonance imaging (MRI) data, including diffusion tensor imaging, were acquired in 16 patients with TRD, who then received SCC DBS. Computerized tomography (CT) was used post-operatively to locate DBS contacts. The activation volume around the contacts used for chronic stimulation was modeled for each patient retrospectively. Probabilistic tractography was used to delineate the white matter tracts traveling through each activation volume. Patient-specific tract maps were calculated using whole-brain analysis. Clinical evaluations of therapeutic outcome from SCC DBS were defined at 6 months and 2 years. Whole-brain activation volume tractography demonstrated that all DBS responders at 6 months (n = 6) and 2 years (n = 12) shared bilateral pathways from their activation volumes to (i) medial frontal cortex via forceps minor and uncinate

fasciculus; (ii) rostral and dorsal cingulate cortex via the cingulum bundle; and (iii) subcortical nuclei. Non-responders did not consistently show these connections. Specific anatomical coordinates of the active contacts did not discriminate responders from non-responders. The authors concluded that patient-specific activation volume tractography modeling may identify critical tracts that mediate SCC DBS antidepressant response, suggesting a novel method for patient-specific target and stimulation parameter selection.

Narang and colleagues (2016) reviewed the English-language literature published between the years 2010 and 2015 regarding the utility of DBS for patients with treatment-refractory depression. The literature review revealed that most DBS research is open label, with few large randomized, placebo-controlled trials to confirm results. Long-term response rates with DBS were between 40% and 70%, with clinical effects depending on location of electrode placement. Improvement was documented to last for months to years. The authors stated that although DBS is potentially effective and a relatively safe option for patients with treatment resistance, it is invasive, costly, and still considered experimental. Understanding of the neurobiology of depression, the mechanism of DBS action, and biomarkers that may predict patient response remains obscure. They stated that future research should contain careful design, including homogenous inclusion criteria and characterization of pre-treatment patient mood, somatic complaints, and cognition; consistent outcome measures; monitoring of depressive symptoms at different brain-positioning targets across an adequate time course; and records of stimulus parameters.

Naesstrom and associates (2016) stated that DBS is a treatment under investigation for a range of psychiatric disorders. It has shown promising results for therapy-refractory OCD and major depressive disorder (MDD). Other indications under investigation include Tourette's syndrome, anorexia nervosa and substance use disorders. These investigators reviewed current studies on psychiatric indications for DBS, with focus on OCD and MDD. They performed a systematic search in Medline, and the literature was searched to identify studies with DBS for psychiatric disorders. The identified studies were analyzed based on patient characteristics, treatment results and AEs of DBS. A total of 52 papers met the inclusion criteria and described a total of 286 unique patients treated with DBS for psychiatric indications;

18 studies described 112 patients treated with DBS for OCD in 6 different anatomical targets, while 9 studies presented 100 patients with DBS for MDD in 5 different targets. The authors concluded that DBS may show promise for treatment-resistant OCD and MDD; but the results were limited by small sample size and insufficient randomized controlled data.

Bergfeld and associates (2016) stated that patients with TRD do not respond sufficiently to several consecutive treatments for major depressive disorder; and DBS is a promising treatment for these patients, but presently placebo effects cannot be ruled out. In a randomized clinical trial, these researchers evaluated the effectiveness of DBS of the ventral anterior limb of the internal capsule (vALIC), controlling for placebo effects with active and sham stimulation phases. A total of 25 patients with TRD from 2 hospitals in the Netherlands were enrolled between March 22, 2010, and May 8, 2014. Patients first entered a 52-week open-label trial during which they received bilateral implants of 4 contact electrodes followed by optimization of DBS until a stable response was achieved. A randomized, double-blind, 12-week cross-over phase was then conducted with patients receiving active treatment followed by sham or vice versa. Response and non-response to treatment were determined using intention-to-treat analyses. The change in the investigator-rated score of the 17-item Hamilton Depression Rating Scale (HAM-D-17) was the main outcome used in analysis of the optimization phase. The primary outcome of the cross-over phase was the difference in the HAM-D-17 scores between active and sham DBS. The score range of this tool is 0 to 52, with higher scores representing more severe symptoms. Patients were classified as responders to treatment (greater than or equal to 50% decrease of the HAM-D-17 score compared with baseline) and partial responders (greater than or equal to 25 but less than 50% decrease of the HAM-D-17 score). Of 25 patients included in the study, 8 (32%) were men; the mean (SD) age at inclusion was 53.2 (8.4) years. Mean HAM-D-17 scores decreased from 22.2 (95% confidence interval [CI]: 20.3 to 24.1) at baseline to 15.9 (95% CI: 12.3 to 19.5) ($p = 0.001$), Montgomery-Asberg Depression Rating Scale scores from 34.0 (95% CI: 31.8 to 36.3) to 23.8 (95% CI: 18.4 to 29.1) ($p < 0.001$), and Inventory of Depressive Symptomatology-Self-report scores from 49.3 (95% CI: 45.4 to 53.2) to 38.8 (95% CI: 31.6 to 46.0) ($p = 0.005$) in the optimization phase. Following the optimization phase, which lasted 51.6 (22.0) weeks, 10 patients (40%) were classified as responders

and 15 individuals (60%) as non-responders; 16 patients entered the randomized cross-over phase (9 responders [56%], 7 non-responders [44%]). During active DBS, patients scored significantly lower on the HAM-D-17 scale (13.6 [95% CI: 9.8 to 17.4]) than during sham DBS (23.1 [95% CI: 20.6 to 25.6]) ($p < 0.001$). Serious adverse events (AEs) included severe nausea during surgery (1 patient), suicide attempt (4 patients), and suicidal ideation (2 patients). The authors concluded that DBS of the vALIC resulted in a significant decrease of depressive symptoms in 10 of 25 patients (40%) and was well-tolerated. The randomized cross-over design corroborated that vALIC DBS causes symptom reduction rather than sham. The main drawbacks of the afore-mentioned study by Bergfeld et al (2016) were discussed by Youngerman and Sheth (2017); and they stated that future work will no doubt take into consideration the important lessons learned in this study.

Saleh and Hasler (2017) noted that DBS for refractory psychiatric disorders shows promising effects on symptom-reduction, however, little is known regarding the effects of DBS on social outcome. These researchers performed a PubMed search based on original studies of DBS for psychiatric disorders [TRD, Gilles de la Tourette's syndrome (GTS), and obsessive compulsive disorder (OCD)]. Data on social outcome following surgery were extracted and analyzed. Social functioning was not a primary outcome measure in the reviewed article. The literature is incomplete and inconclusive on this variable, however from the reported data, there is some evidence that DBS has the potential to improve social functioning. The authors concluded that more systematic and detailed data gathering and reporting on social outcome with longer follow-ups are needed to evaluate more exhaustively the role of DBS in refractory psychiatric disorders.

Furthermore, an UpToDate review on “Unipolar depression in adults: Treatment of resistant depression” (Thase and Connolly, 2017) does not mention DBS as a therapeutic option.

Riva-Posse et al (2018) stated that target identification and contact selection are known contributors to variability in efficacy across different clinical indications of DBS surgery. These researchers carried out a retrospective analysis of responders to SCC DBS for depression demonstrated the common impact of the electrical stimulation on a stereotypic connectome of converging white matter bundles (forceps

minor, uncinate fasciculus, cingulum and fronto-striatal fibers). To test the utility of a prospective, connectomic approach for SCC DBS surgery, this pilot study used the 4-bundle tractography "connectome blueprint" to plan surgical targeting in 11 participants with TRD. Before surgery, targets were selected individually using deterministic tractography. Selection of contacts for chronic stimulation was made by matching the post-operative probabilistic tractography map to the pre-surgical deterministic tractography map for each subject. Intra-operative behavioral responses were used as a secondary verification of location. A probabilistic tract map of all participants demonstrated inclusion of the 4 bundles as intended, matching the connectome blueprint previously defined; 8 of 11 patients (72.7 %) were responders and 5 were remitters after 6 months of open-label stimulation. At 1 year, 9 of 11 patients (81.8 %) were responders, with 6 of them in remission. The authors concluded that these results supported the use of a group probabilistic tractography map as a connectome blueprint for individualized, patient-specific, deterministic tractography targeting, confirming retrospective findings previously published. This new method represented a connectomic approach to guide future SCC DBS studies.

The authors stated that while their findings could not explain the reasons for failed RCTs of this or other DBS targets for neuropsychiatric disorders, these findings supported the use of tractography-based surgical targeting to reduce variability in the direct effects of stimulation on the patient-specific brain circuitry. They proposed that their new methodology enables more consistent and precise modulation of a pre-defined collection of axonal pathways in all study subjects. This strategy allowed a more controlled analysis of the population and streamlined the stimulation programming. Standardization of targeting and programming algorithms informed by these results may help to refine study design and interpretation of outcomes of future studies.

Crowell et al (2019) stated that SCC DBS has been studied as a potential treatment for severe and refractory major depressive disorder since 2005. In an open-label, long-term follow-up study, these investigators examined subjects enrolled in a clinical trial of SCC DBS for treatment-resistant depression. Long-term outcome data were collected for 28 patients (20 with MDD and 7 with bipolar II disorder; 1 patient in the MDD subgroup was later re-classified as having bipolar II

disorder) receiving SCC DBS for 4 to 8 years. Response and remission rates were maintained at greater than or equal to 50 % and greater than or equal to 30 %, respectively, through years 2 to 8 of the follow-up period; 75 % of all subjects met the treatment-response criterion for more than 50 % of their duration of participation in the study, with 21 % of all patients demonstrating continuous response to treatment from the 1st year onward. Of 28 participants, 14 completed greater than or equal to 8 years of follow-up, 11 completed greater than or equal to 4 years, and 3 dropped out before 8 years. The procedure itself was generally safe and well-tolerated, and there were no side effects of acute or chronic stimulation. The rate of medical or surgical complications was consistent with the rate observed in studies of DBS for other indications. There were no suicides. The authors concluded that in over 8 years of observation, most subjects experienced a robust and sustained antidepressant response to SCC DBS. Moreover, these researchers stated that larger blinded, controlled trials are needed to validate the safety and efficacy of SCC DBS. The 1st such trial failed to show a statistically significant difference between active (17 %) and sham (22 %) stimulation at the pre-defined 6-month endpoint, but a progressive increased response rate of 53 % and 49 % with open-label stimulation at 18 and 24 months, respectively, was observed. They stated that these results supported a re-assessment of clinical trial designs for studies of DBS for TRD, in order to conduct trials that will examine not only short-term efficacy but meaningful, sustained response over the long-term.

Wu et al (2021) stated that DBS has shown promising outcomes as new therapeutic opportunities for patients with TRD who do not respond adequately to several consecutive treatments. In a systematic review and meta-analysis, these researchers examined the safety and efficacy of DBS for TRD. literature was comprehensively reviewed using Medline, Google scholar, Cochrane library, Embase, and World Health Organization International Clinical Trials Registry Platform until January 2019. The studied outcomes included response, remission, recurrence, and AEs rates, and were reported as the rate ratio (RR) or pooled estimate with a 95 % confidence interval (95 % CI). Heterogeneity was measured by an I-square (I2) test and a sensitive analysis. A total of 17 studies involving 7 DBS targets were included. For efficacy, DBS treatment was statistically beneficial for TRD, and the response, remission, and recurrence rates were 56 % (ranging from 43 % to 69 %), 35 % (ranging from 27 % to 44 %), and 14 % (ranging from

4 % to 2 5%), respectively. However, only 2 RCTs considered the invalidity of DBS (RR = 1.45, 95 % CI: 0.50 to 4.21). For safety, the AEs rate was 67 % (ranging from 54 % to 80 %). The AEs were common and moderate, but the problems related to suicide and suicidal ideation should not be under-estimated. The authors concluded that these findings suggested that DBS for TRD is considered promising, which should be confirmed by well-designed and large sample studies. These researchers stated that future basic research and comprehensive clinical trials are needed to reach better understanding on the mechanisms of action and optimal targeted structure.

UpToDate reviews on “Unipolar depression in adults: Choosing treatment for resistant depression” (Thase and Connolly, 2021a), and “Unipolar depression in adults: General principles of treating resistant depression” (Thase and Connolly, 2021b) do not mention DBS as a management / therapeutic option.

Furthermore, an UpToDate review on “Unipolar depression in adults: Management of highly resistant (refractory) depression” (Thase and Connolly, 2021c) states that “Our definition of treatment refractory depression is drawn in part from the inclusion criteria for studies of investigational treatments such as deep brain stimulation and ablative neurosurgery …The most widely studied surgical intervention is deep brain stimulation; however, in the one randomized trial that has been conducted, deep brain stimulation was not beneficial for refractory depression … Patients with severe, intractable, and disabling unipolar major depression may be candidates for clinical trials investigating neurosurgical interventions, including deep brain stimulation and direct cortical stimulation”.

Runia et al (2023) stated that DBS is a promising intervention for the management of patients with TRD. Effects on cognitive functioning are unclear since they have been studied in small samples. In a systematic review and meta-analyses, these researchers examined the impact of DBS on cognitive functioning in TRD. They included 10 studies that compared standardized neuropsychological tests before and after DBS or between active and sham DBS in TRD. Different random-effects meta-analyses were carried out for different cognitive (sub-)domains and for different follow-up time windows (less than 6 months, 6 to 18 months, and greater than 18 months). These

researchers found no significant differences in cognitive functioning up to 6 months of DBS. After 6 to 18 months of DBS small-to-moderate improvements were found in verbal memory (Hedge's g = 0.22, 95 % CI: 0.01 to 0.43]=, p = 0.04), visual memory (Hedge's g = 0.37, 95 % CI: 0.03 to 0.71, p = 0.04), attention/psychomotor speed (Hedge's g = 0.26, 95 % CI: 0.02 to 0.50, p = 0.04) and executive functioning (Hedge's g = 0.37, 95 % CI: 0.15 to 0.59, p = 0.001). Not enough studies could be retrieved for a meta-analysis of effects after greater than 18 months of DBS or for the comparison of active and sham DBS. The authors concluded that qualitatively, generally no differences in cognitive functioning between active and sham DBS were found. No cognitive decline was found in this meta-analysis up to 18 months of DBS in patients with TRD. Results even suggest small positive effects of DBS on cognitive functioning in TRD, although this should be interpreted with caution due to lack of controlled data.

Cluster Headaches

In an uncontrolled, open-label, prospective study, Akram and colleagues (2016) presented outcomes in a cohort of medically intractable chronic cluster headache (CCH) patients treated with ventral tegmental area (VTA) DBS. A total of 21 patients (17 males; mean age of 52 years) with medically refractory CCH were selected for ipsilateral VTA-DBS by a specialist multi-disciplinary team including a headache neurologist and functional neurosurgeon. Patients had also failed or were denied access to occipital nerve stimulation within the UK National Health Service. The primary end-point was improvement in the headache frequency; secondary outcomes included other headache scores (severity, duration, headache load), medication use, disability and affective scores, quality of life (QOL) measures, and AEs. Median follow-up was 18 months (range of 4 to 60 months). At the final follow-up point, there was 60% improvement in headache frequency (p = 0.007) and 30% improvement in headache severity (p = 0.001). The headache load (a composite score encompassing frequency, severity, and duration of attacks) improved by 68% (p = 0.002). Total monthly triptan intake of the group dropped by 57% post-treatment. Significant improvement was observed in a number of QoL, disability, and mood scales; AEs included diplopia, which resolved in 2 patients following stimulation adjustment, and persisted in 1 patient with a history of ipsilateral trochlear nerve palsy. There were no other serious AEs. The authors concluded that the findings of this study supported that VTA-DBS may be a safe and effective therapy for refractory CCH patients

who failed conventional treatments. (Class IV Evidence). The main drawbacks of this study were its open-label design (a placebo effect cannot be excluded) and its small sample size (n = 21). These findings need to be validated by well-designed studies.

Autism Spectrum Disorder and Self-Injurious Behavior

Park and colleagues (2017) examined the clinical outcome of DBS for autism spectrum disorder (ASD) and the functional and structural changes in the brain after DBS. These researchers presented the case of a 14-year old boy with ASD and self-injurious behavior (SIB) refractory with medical and behavioral therapy. He was treated by bilateral nucleus accumbens (NAc) DBS. Remarkable clinical improvement was observed following NAc DBS. Brain fluorodeoxyglucose-positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI) volumetric studies revealed that the metabolism in the prefrontal and the frontal cortex as well as the occipital cortex was markedly decreased in association with the decreased cortical volumes in those areas 2 years after NAc DBS. The authors noted the therapeutic potential of NAc DBS for the improvement of patients with ASD and SIB with structural and functional changes after DBS. These preliminary findings need to be validated by well-designed studies.

Explosive Aggressive Behavior

Giordano et al (2016) stated that intermittent explosive disease (IED) is a psychiatric disorder characterized by intermittent attacks of rage and violence frequently resistant to pharmacological therapy. Deep brain stimulation of the postero-medial hypothalamus has been applied with fair results and clinical improvement with some surgical morbidity due to neuro-vegetative side effects. The anterior limb of the internal capsule/ventral capsule/ventral striatum (VC/VS) has never been used alone as a target for this disease. These researchers evaluated the effectiveness of bilateral DBS of the VC/VS for the treatment of IED. They performed bilateral DBS of the VC/VS in a 21-year old patient with IED. This young man had a traumatic birth complicated by hypoxia, and he showed a mild mental impairment. Different pharmacological treatments were carried out with no results before DBS was proposed to the patient's relatives after multi-disciplinary approval. After 22 months of high-frequency mono-polar bilateral DBS of the VC/VS, the patient showed a significant improvement. Post-

operative 18F-FDG PET-CT studies ruled out a reduction of the hyper-metabolic areas located in the limbic system previously detected in pre-operative investigations. The authors concluded that bilateral DBS of the VC/VS may be considered for the treatment of IED without the risk of neuro-vegetative side effects. These preliminary findings need to be validated by well-designed studies.

Orthostatic Tremor

In a large case-series study, Hassan and associates (2016) evaluated the clinical, electrophysiological, and treatment outcome features of orthostatic tremor (OT). These investigators performed medical record review of 184 patients who met clinical and electrodiagnostic criteria for OT from 1976 to 2013 at the Mayo Clinic; demographic, clinical, electrophysiological, and treatment data were extracted. The majority of OT cases were female (63.6%) and mean age at onset was 59.3 years (range of 13 to 85). Diagnosis was delayed by a mean of 7.2 years (range of 0 to 44). The average tremor frequency was 15.7 Hz (range of 12.5 to 20), and transmitted to the arms on weight-bearing (95.5%). Patients reported a spectrum of progressive orthostatic leg symptoms, relieved by sitting or leaning. Falls were reported in 24.1%. Co-existent neurologic disorders included essential tremor (22.8%), other tremor (4.9%), and Parkinsonism (8.7%). Family history of OT was noted in 4.9%. Of 46 medications trialed, 24 failed to provide any benefit. Benzodiazepines provided at least mild benefit in 55.9%, and moderate to marked benefit in 31.5%; β-blockers (31.0%) and anticonvulsants (25.0%) provided mild benefit, and the remainder were largely ineffective. Medication benefit waned over time; DBS was effective in 2 cases. The authors concluded that OT predominantly affects female seniors, and the diagnosis should be considered with any orthostatic-induced leg symptoms, and confirmed by surface electromyography. They stated that benzodiazepines are the most effectives treatment, followed by beta-blockers and anti-convulsants; the published experience with DBS for OT is too limited at present to form definite conclusions, DBS should be further explored for treatment.

Hewitt and colleagues (2019) noted that OT is a high-frequency weight-bearing tremor of the legs and trunk associated with progressive disability and is often refractory to medications. Case reports suggested that thalamic DBS is effective. These investigators reported 5 female patients with medication-refractory OT who underwent

bilateral thalamic DBS at the Mayo Clinic and evaluated factors associated with a successful DBS outcome. Demographic, clinical, electrophysiology, and DBS data were abstracted. Outcomes were change in tremor-onset latency, standing time, standing ADLs, and patient and clinician global impression of change (PGIC; CGIC). All 5 patients had improved standing time (72 versus 408 seconds, $p \leq 0.001$) and improved standing ADLs after surgery, without change in tremor-onset latency (16 versus 75 seconds, $p = 0.14$). Maximal benefit was reached up to 3 years after surgery and sustained for up to 6 years. CGIC was "much improved" in all; PGIC was "much improved" in 4 and "minimally improved" in 1. There were no major complications; and post-operative electrophysiology (n = 1) showed lower tremor amplitude and slower tremor ramp-up on versus off stimulation. The authors concluded that bilateral thalamic DBS improved OT symptoms with benefit lasting up to 6 years. A modest increase in standing time of several minutes was associated with meaningful improvement in standing ADLs. Microlesional effect and bilateral stimulation are likely favorable features, while baseline standing time of several minutes may be unfavorable. These researchers stated that these findings may inform clinician and patient counseling and require confirmation in larger studies.

Post-Traumatic Tremor

Rojas-Medina et al (2016) noted that post-traumatic tremor (PTT) is the most frequent movement disorder secondary to cranioencephalic trauma and can be persistent and disabling. These investigators reviewed and evaluated the effectiveness of DBS at the VIM/VOP/ZI (ventralis intermedius/ventrooralis posterior/zona incerta) complex level for the treatment of PTT. During the period from 1999 to 2014, a total of 5 patients diagnosed with PTT were selected who had experienced a major deterioration in their QoL without improvement during medical treatment for more than 1 year. They underwent surgery for DBS at the VIM/VOP/ZI complex level, and the modified tremor scale before and after surgery was used for their follow-up. Each patient showed improvements in their symptoms after DBS compared with baseline, which was moderate (II) in 2 cases and marked (III) in the other cases. All of the improvements were maintained with chronic DBS, without tremor rebound. The authors concluded that stimulation of the contralateral VIM/VOP/ZI complex resulted in a noticeable

improvement in tremor and recovery of independence in basic daily activities in patients with PTT. These preliminary findings need to be validated by well-designed studies.

Traumatic Brain Injury

Schiff (2016) discussed a general rationale for the use of central thalamic DBS (CT-DBS) to support arousal regulation mechanisms in the severely injured brain. The organizing role of the anterior forebrain mesocircuit in recovery mechanisms following widespread deafferentation produced by multi-focal structural brain injuries was emphasized. The mesocircuit model provides the conceptual foundation for the key role of the central thalamus as a privileged node for neuromodulation to support forebrain arousal regulation. In this context, cellular mechanisms arising at the neocortical, striatal, and thalamic population level are considered in the assessment of an individual patient's capacity for harboring underlying reserve that could be recruited for further recovery. The author noted that recent pre-clinical studies and pilot clinical results were compared to frame the detailed rationale for CT-DBS. Application of CT-DBS across the range of outcomes following severe-to-moderate brain injuries was discussed with the aim of improving consciousness and cognition in patients with non-progressive brain injuries.

Disorders of Consciousness

Vanhoecke and Hariz (2017) stated that a treatment for patients suffering from prolonged severely altered consciousness is not available. The success of DBS in diseases such as dystonia, essential tremor and PD provided a renewed impetus for its application in disorders of consciousness (DoC). These researchers evaluated the rationale for DBS in patients with DoC, through systematic review of literature containing clinical data and ethical considerations. Articles from PubMed, Embase, Medline and Web of Science were systematically reviewed. The outcomes of 78 individual patients reported in 19 articles from 1968 onwards were pooled and elements of ethical discussions were compared. There is no clear clinical evidence that DBS is a treatment for DoC that can restore both consciousness and the ability to communicate. In patients who benefitted, the outcome of DBS is often confounded by the time frame of spontaneous recovery from DoC. Difficult ethical considerations remain, such as the risk of increasing self-awareness of own limitations, without improving overall

well-being, and the issues of proxy consent. The authors concluded that DBS is far from being evident as a possible future therapeutic avenue for patients with DoC. They stated that double-blind studies are lacking, and many clinical and ethical issues have to be addressed.

Rezaei and colleagues (2019) noted that MCS is a disorder of consciousness in which minimal but definite behavioral evidence of self-awareness or environmental awareness is demonstrated; and DBS of various targets has been used to promote recovery in patients with disorders of consciousness with varying results. In a systematic review, these researchers examined the effects of DBS in MCS following traumatic brain injury (TBI). A systematic literature review was carried out using a number of electronic bibliographic data bases to identify relevant studies. These investigators included all studies describing applications of DBS on patients in MCS following TBI. A total of 8 studies were identified, including 10 patients, aged 15 to 58 years. The time from injury to stimulation ranged from 3 to 252 months, with the duration of follow-up post-DBS ranging from 10 to 120 months; 7 patients improved their post-surgical outcome score measures (3 patients with the coma recovery scale, 1 with the near coma scale, and 3 with the Glasgow outcome score). A descriptive favorable outcome was reported in 1 patient; 2 patients were reported not to have shown any improvements following the intervention. The authors concluded that current evidence is based on a small population of heterogeneous patients. The time from injury to stimulation was significantly variable and problematic, as spontaneous recovery could occur within the first year of injury. These researchers stated that although 7 patients showed promising results in validated outcome measures, evidence supporting the use of DBS in MCS patients following TBI is lacking. They stated that there is need for RCTs.

Wu et al (2023) noted that the use of SCS and DBS for DoC has been increasingly reported; however, there is insufficient evidence to determine safety and effectiveness of SCS and DBS for the management of DoC owing to various methodological limitations. In a systematic review, these investigators examined the safety and effectiveness of SCS and DBS for DoC by reviewing related literature by searching PubMed, Embase, Medline, and Cochrane Library. A total of 20 eligible studies with 608 patients were included in this study – 10 studies with 508 patients reported the effectiveness of SCS for DoC, and the estimated overall effectiveness rate was 37 % ; 5 studies with

343 patients reported the effectiveness of SCS for VS, and the estimated effectiveness rate was 30 %; 3 studies with 53 patients reported the effectiveness of SCS for MCS, and the estimated effectiveness rate was 63 %; 5 studies with 92 patients reported the effectiveness of DBS for DoC, and the estimated overall effectiveness rate was 40 %; 4 studies with 63 patients reported the effectiveness of DBS for VS, and the estimated effectiveness rate was 26 %; 3 studies with 19 patients reported the effectiveness of DBS for MCS, and the estimated effectiveness rate was 74 %. The AE rate of DoC was 8.1 % and 18.2 % after SCS and DBS, respectively. The authors concluded that these findings suggested that SCS and DBS could be considered reasonable treatments for DoC with considerable safety and effectiveness.

Refractory Epilepsy

Fisher et al (2010) reported a multi-center, double-blind, randomized trial of bilateral stimulation of the anterior nuclei of the thalamus for localization-related epilepsy. Subjects were adults with medically refractory partial seizures, including secondarily generalized seizures. Half received stimulation and half no stimulation during a 3-month blinded phase; then all received unblinded stimulation. A total of 110 subjects were randomized. Baseline monthly median seizure frequency was 19.5. In the last month of the blinded phase the stimulated group had a 29% greater reduction in seizures compared with the control group, as estimated by a generalized estimating equations (GEE) model ($p = 0.002$). Unadjusted median declines at the end of the blinded phase were 14.5% in the control group and 40.4% in the stimulated group. Complex partial and "most severe" seizures were significantly reduced by stimulation. By 2 years, there was a 56% median percent reduction in seizure frequency; 54% of patients had a seizure reduction of at least 50%, and 14 patients were seizure-free for at least 6 months. Five deaths occurred and none was from implantation or stimulation. No subject had symptomatic hemorrhage or brain infection. Two subjects had acute, transient stimulation-associated seizures. Cognition and mood showed no group differences, but subjects in the stimulated group were more likely to report depression or memory problems as adverse events. The authors concluded that bilateral stimulation of the anterior nuclei of the thalamus reduces seizures. Benefit persisted for 2 years of study. Complication rates were modest. They stated that DBS of the anterior thalamus is useful for some people with medically refractory partial and

secondarily generalized seizures. More studies are needed to determine whether this approach can result in long-term benefits. In this regard, it was noted that "[t]he FDA recently requested that the Medtronic Deep Brain Stimulation (DBS) Therapy ... undergo a second phase 3 study, even though a first was positive, and even though an FDA advisory panel recommended the device's outright approval, so they are taking a cautious stance. There is also a great deal to be learned about selection of the most appropriate patients, and selection of stimulation parameters that would optimize efficacy" (Collins, 2010).

Fountas et al (2010) reviewed the pertinent literature to outline the role of cerebellar stimulation (CS) in the management of medically refractory epilepsy. The PubMed medical database was systematically searched for the following terms: "cerebellar," "epilepsy," "stimulation," and "treatment," and all their combinations. Case reports were excluded from this study. The pertinent articles were categorized into 2 large groups: animal experimental and human clinical studies. Particular emphasis on the following aspects was given when reviewing the human clinical studies: their methodological characteristics, the number of participants, their seizure types, the implantation technique and its associated complications, the exact stimulation target, the stimulation technique, the seizure outcome, and the patients' psychological and social post-stimulation status. Three clinical double-blind studies were found, with similar implantation surgical technique, stimulation target, and stimulation parameters, but quite contradictory results. Two of these studies failed to demonstrate any significant seizure reduction, whereas the third one showed a significant post-stimulation decrease in seizure frequency. All possible factors responsible for these differences in the findings are analyzed in the present study. The authors concluded that CS seems to remain a stimulation target worth exploring for defining its potential in the treatment of medically intractable epilepsy, although the data from the double-blind clinical studies that were performed failed to establish a clear benefit in regard to seizure frequency. They stated that a large-scale, double-blind clinical study is needed for accurately defining the efficacy of CS in epilepsy treatment.

Sprengers et al (2014) evaluated the efficacy, safety and tolerability of DBS and cortical stimulation for refractory epilepsy based on RCTs. These investigators searched PubMed (August 6, 2013), the Cochrane Epilepsy Group Specialized Register (August 31, 2013), Cochrane

Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 7 of 12) and reference lists of retrieved articles. They also contacted device manufacturers and other researchers in the field. No language restrictions were imposed. Randomized controlled trials comparing DBS or cortical stimulation to sham stimulation, resective surgery or further treatment with anti-epileptic drugs were selected for analysis. Four review authors independently selected trials for inclusion. Two review authors independently extracted the relevant data and assessed trial quality and overall quality of evidence. The outcomes investigated were seizure freedom, responder rate, percentage seizure frequency reduction, adverse events, neuropsychological outcome and quality of life. If additional data were needed, the study investigators were contacted. Results were analyzed and reported separately for different intra-cranial targets for reasons of clinical heterogeneity. A total of 10 RCTs comparing 1 to 3 months of intra-cranial neurostimulation to sham stimulation were identified. One trial was on anterior thalamic DBS (n = 109; 109 treatment periods); 2 trials on centro-median thalamic DBS (n = 20; 40 treatment periods), but only one of the trials (n = 7; 14 treatment periods) reported sufficient information for inclusion in the quantitative meta-analysis; 3 trials on cerebellar stimulation (n = 22; 39 treatment periods); 3 trials on hippocampal DBS (n = 15; 21 treatment periods); and 1 trial on responsive ictal onset zone stimulation (n = 191; 191 treatment periods). Evidence of selective reporting was present in 4 trials and the possibility of a carryover effect complicating interpretation of the results could not be excluded in 4 cross-over trials without any washout period. Moderate-quality evidence could not demonstrate statistically or clinically significant changes in the proportion of patients who were seizure-free or experienced a 50% or greater reduction in seizure frequency (primary outcome measures) after 1 to 3 months of anterior thalamic DBS in (multi) focal epilepsy, responsive ictal onset zone stimulation in (multi) focal epilepsy patients and hippocampal DBS in (medial) temporal lobe epilepsy. However, a statistically significant reduction in seizure frequency was found for anterior thalamic DBS (-17.4% compared to sham stimulation; 95% CI: -32.1 to -1.0; high-quality evidence), responsive ictal onset zone stimulation (-24.9%; 95% CI: -40.1 to 6.0; high-quality evidence)) and hippocampal DBS (-28.1%; 95% CI: -34.1 to -22.2; moderate-quality evidence). Both anterior thalamic DBS and responsive ictal onset zone stimulation do not have a clinically meaningful impact on quality life after 3 months of stimulation (high-quality evidence). Electrode

implantation resulted in asymptomatic intracranial hemorrhage in 3% to 4% of the patients included in the 2 largest trials and 5% to 13% had soft tissue infections; no patient reported permanent symptomatic sequelae. Anterior thalamic DBS was associated with fewer epilepsy-associated injuries (7.4 versus 25.5%; p = 0.01) but higher rates of self-reported depression (14.8 versus 1.8%; p = 0.02) and subjective memory impairment (13.8 versus 1.8%; p = 0.03); there were no significant differences in formal neuropsychological testing results between the groups. Responsive ictal-onset zone stimulation was well-tolerated with few side effects but SUDEP rate should be closely monitored in the future (4 per 340 [= 11.8 per 1,000] patient-years; literature: 2.2-10 per 1,000 patient-years). The limited number of patients preclude firm statements on safety and tolerability of hippocampal DBS. With regards to centro-median thalamic DBS and cerebellar stimulation, no statistically significant effects could be demonstrated but evidence is of only low to very low quality. The authors concluded that only short-term RCTs on intra-cranial neurostimulation for epilepsy are available. Compared to sham stimulation, 1 to 3 months of anterior thalamic DBS ((multi) focal epilepsy), responsive ictal onset zone stimulation ((multi) focal epilepsy) and hippocampal DBS (temporal lobe epilepsy) moderately reduce seizure frequency in refractory epilepsy patients. Anterior thalamic DBS is associated with higher rates of self-reported depression and subjective memory impairment. SUDEP rates require careful monitoring in patients undergoing responsive ictal onset zone stimulation. They stated that there is insufficient evidence to make firm conclusive statements on the efficacy and safety of hippocampal DBS, centro-median thalamic DBS and cerebellar stimulation; and there is a need for more, large and well-designed RCTs to validate and optimize the efficacy and safety of invasive intra-cranial neurostimulation treatments.

Salanova et al (2015) reported long-term efficacy and safety results of the SANTE trial investigating DBS of the anterior nucleus of the thalamus (ANT-DBS) for the treatment of drug-resistant partial epilepsy. This long-term follow-up was a continuation of a previously reported trial of 5- versus 0-V ANT stimulation. Long-term follow-up began 13 months after device implantation with stimulation parameters adjusted at the investigators' discretion. Seizure frequency was determined using daily seizure diaries. The median percent seizure reduction from baseline at 1 year was 41%, and 69% at 5 years. The responder rate

(greater than or equal to 50% reduction in seizure frequency) at 1 year was 43%, and 68% at 5 years. In the 5 years of follow-up, 16% of subjects were seizure-free for at least 6 months. There were no reported unanticipated adverse device effects or symptomatic ICH. The Liverpool Seizure Severity Scale and 31-item Quality of Life in Epilepsy measure showed statistically significant improvement over baseline by 1 year and at 5 years ($p < 0.001$). The authors concluded that long-term follow-up of ANT-DBS showed sustained efficacy and safety in a treatment-resistant population.

Piacentino et al (2015) stated that drug-resistant epileptic patients account for 40% of cases of epilepsy. Consequently, specific therapeutic options could be surgical resection or, if not indicated, DBS. These investigators reviewed data from patients affected by drug-resistant complex partial epilepsy with or without generalization treated by ANT-DBS to evaluate the efficacy and potential future applications of this approach as a standard method for palliative seizure control. A total of 6 patients affected by drug-resistant complex partial seizures underwent AN DBS from March 2007 to February 2011. The pre-operative tests consisted of electroencephalography (EEG), video EEG, morphologic and functional magnetic resonance imaging (MRI), non-acute positron emission tomography (PET), neuropsychological evaluation, Liverpool seizure scale, and Quality Of Life In Epilepsy (QOLIE). These tests and a seizure diary were also administered during a follow-up of at least 3 years. The improvement in terms of decrease of seizures was more than 50% in patients affected by complex partial seizures strictly related to limbic system origin. The amelioration was unsatisfactory for patients having anatomical lesions outside the limbic structures with evidence of late diffusion in limbic areas; 1 patient died 40 days after surgery for reasons not concerned with DBS. The authors concluded that although the small number of enrolled patients limited the reliability of data, the results were in accordance with those found in the recent literature and deserve to be considered for further studies regarding real efficacy, indications, stimulation parameters, side effects, and complications.

Kim et al (2017) evaluated the long-term safety and efficacy of ATN-DBS treatment, as well as predictors of its success, in patients with drug-refractory epilepsy (DRE). These investigators retrospectively studied clinical outcomes in 29 consecutive refractory epilepsy patients treated by a single DBS team (2 neurosurgeons, 4 neurologists) over

an 11-year period, for whom follow-up was performed for up to 137 months (mean of 74.9 months). The average participant was 30.7 (± 10.4) years old and had epilepsy for 19.3 (± 9.0) years. The mean pre-operative frequency of disabling partial or generalized tonic-clonic seizures was 27.5 (± 8.6, SE) seizures a month. The median percent seizure reduction was 71.3% at 1year, 73.9% at 2 years, and ranged from 61.8% to 80.0% over post-implant years 3 through 11 in the long-term study (overall 70% median reduction). In the 11-year study period, 13.8% (4/29) of subjects were seizure-free for at least 12 months during this time. There was only 1 symptomatic ICH that happened during follow-up (3.4%). Infection requiring removal and later re-implantation of hardware occurred in only 1 of 30 patients (3.3%), who was subsequently excluded from follow-up assessment. Hardware malfunction including lead disconnection occurred in 2 of 29 cases (6.9%). Revision of lead position to redeem poor clinical response was performed in 3 of 58 implanted leads (5.2%). The authors concluded that ATN-DBS can be an effective therapy in a variety of patients with DRE. They provided evidence that significant therapeutic efficacy can be sustained for up to 11 years. Neurological complications were rather rare, but long-term hardware-related complications should be closely followed.

Chang and Xu (2018) noted that conflicting conclusions have been reported regarding predictors of DBS outcome in patients with refractory temporal lobe epilepsy (TLE). The main goal of this meta-analysis study was to identify possible predictors of remarkable seizure reduction (RSR). These investigators conducted a comprehensive search of English-language literature published since 1990 and indexed in PubMed, Embase, and the Cochrane Library that addressed seizure outcomes in patients who underwent DBS for refractory TLE. A pooled RSR rate was determined for eight included studies; RSR rates were analyzed relative to potential prognostic variables. Random- or fixed-effects models were used depending on the presence or absence of heterogeneity. The pooled RSR rate among 61 DBS-treated patients with TLE from 8 studies was 59%. Higher likelihood of RSR was found to be associated with lateralization of stimulation, lateralized ictal EEG findings, and a longer follow-up period. Seizure semiology, MRI abnormalities, and patient sex were not predictive of RSR rate. The best electrode type for RSR was the Medtronic 3389. Hippocampal and anterior thalamic nuclei (ATN) sites of stimulation had similar odds of producing RSR. The authors concluded that DBS is an effective

therapeutic modality for intractable TLE, particularly in patients with lateralized EEG abnormalities and in patients treated on the ictal side. This meta-analysis provided evidence-based information for determining DBS suitability in pre-surgical counseling and for explaining seizure outcomes.

Bouwens van der Vlis et al (2019) stated that despite the use of 1st-line anti-epileptic drugs and satisfactory seizure outcome rates after resective epilepsy surgery, a considerable percentage of patients do not become seizure-free; and ANT-DBS may provide an alternative therapeutic option in these patients. These investigators discussed the rationale, mechanism of action, clinical efficacy, safety, and tolerability of ANT-DBS in drug-resistant epilepsy (DRE) patients. A review using systematic methods of the available literature was performed using relevant databases including Medline, Embase, and the Cochrane Library pertaining to the different aspects ANT-DBS. ANT-DBS for drug-resistant epilepsy is a safe, effective and well-tolerated therapy, where a special emphasis must be given to monitoring and neuropsychological assessment of both depression and memory function. Three patterns of seizure control by ANT-DBS are recognized, of which a delayed stimulation effect may account for an improved long-term response rate. ANT-DBS remotely modulates neuronal network excitability through over-riding pathological electrical activity, decrease neuronal cell loss, through immune response inhibition or modulation of neuronal energy metabolism. ANT-DBS is an efficacious treatment modality, even when curative procedures or lesser invasive neuromodulative techniques failed. When compared to VNS, ANT-DBS showed slightly superior treatment response, which urges for direct comparative trials. Based on the available evidence ANT-DBS and VNS therapies are currently both superior compared to non-invasive neuromodulation techniques such as t-VNS and rTMS.

On April 27, 2018, the FDA approved (via the PMA process) the Medtronic DBS System (bilateral stimulation of the anterior nucleus of the thalamus) as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to 3 or more anti-epileptic medications. The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness in patients who averaged 6 or more seizures per month over the 3 most recent months prior to

implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures (Voelker, 2018). Implantation of a DBS system is contraindicated for diathermy, MRI using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area, and transcranial magnetic stimulation.

Klinger and Mittal (2018) noted that anti-epileptic drugs prevent morbidity and death in a large number of patients suffering from epilepsy. However, it is estimated that approximately 30% of epileptic patients will not have adequate seizure control with medication alone. Resection of epileptogenic cortex may be indicated in medically refractory cases with a discrete seizure focus in non-eloquent cortex. For patients in whom resection is not an option, DBS may be an effective means of seizure control. Deep brain stimulation targets for treating seizures primarily include the thalamic nuclei, hippocampus, sub-thalamic nucleus, and cerebellum. A variety of stimulation parameters have been studied, and more recent advances in electrical stimulation to treat epilepsy include responsive neuro-stimulation. The authors concluded that data suggested that DBS is effective for treating DRE.

Zhou et al (2018b) stated that the field of DBS for epilepsy has grown tremendously since its inception in the 1970s and 1980s. These investigators evaluated all studies published on the topic of open-loop DBS for epilepsy over the past decade (2008 to present). A PubMed search was conducted to identify all articles reporting clinical outcomes of open-loop DBS for the treatment of epilepsy published since January 1, 2008. The following composite search terms were used: ("epilepsy" [MeSH] OR "seizures" [MeSH] OR "kindling, neurologic" [MeSH] OR epilep* OR seizure* OR convuls*) AND ("deep brain stimulation" [MeSH] OR "deep brain stimulation" OR "DBS") OR ("electric stimulation therapy" [MeSH] OR "electric stimulation therapy" OR "implantable neurostimulators" [MeSH]). The authors identified 41 studies that met the criteria for inclusion. The ANT, centro-median nucleus of the thalamus, and hippocampus were the most frequently evaluated targets. Among the 41 articles, 19 reported on stimulation of the ANT, 6 evaluated stimulation of the centro-median nucleus of the thalamus, and 9 evaluated stimulation of the hippocampus. The remaining 7 articles reported on the evaluation of alternative DBS

targets, including the posterior hypothalamus, sub-thalamic nucleus, ventral intermediate nucleus (VIN) of the thalamus, nucleus accumbens, caudal zone incerta, mammillo-thalamic tract, and fornix. The authors evaluated each study for overall epilepsy response rates as well as adverse events (AEs) and other significant, non-epilepsy outcomes. The authors concluded Level I evidence supports the safety and efficacy of stimulating the ANT and the hippocampus for the treatment of medically refractory epilepsy. Level III and IV evidence supports stimulation of other targets for epilepsy.

Furthermore, an UpToDate review on “Evaluation and management of drug-resistant epilepsy” (Sirven, 2018) states that “Deep brain stimulation -- In a randomized clinical trial of deep brain stimulation in the anterior nucleus of the thalamus (SANTE trial) in 110 patients with drug-resistant epilepsy, stimulation therapy was associated with a 29% reduction in seizure frequency compared with sham stimulation at 3 months; 54% of patients had a seizure reduction of at least 50% by 2 years in the unblinded phase. Complex partial and "most severe" seizures were most significantly reduced by stimulation. Participants in the stimulated group were more likely to report depression (15 versus 2%) and memory problems (13 versus 2%) as adverse effects. There were five asymptomatic hemorrhages (5%) and 14 implant site infections (13%). In a long-term follow-up study of the same trial, the responder rate was 68% at 5 years in 59 continuing patients with complete seizure diary information. Measures of seizure severity and quality of life also improved over time. There were no unanticipated adverse events with extended follow up, and rates of depression, suicidality, and SUDEP were comparable to expected rates in the general refractory epilepsy population. The device was approved by the US Food and Drug Administration in 2018 as adjunctive therapy for adults with partial-onset seizures who are refractory to 3 or more antiseizure drugs. It was previously approved for refractory epilepsy elsewhere, including in Europe, Canada, and Australia”.

Troster and colleagues (2017) examined incidence of memory and depression AE in the SANTE Trial blinded phase and their relationship to objective neurobehavioral measures, baseline characteristics, QOL and long-term neurobehavioral outcome. The neurobehavioral AE and neuropsychological data from the SANTE Trial were analyzed. Reliable change indices (RCI) were calculated for memory and mood measures. Analyses examined relationships among AEs, RCIs,

demographic and seizure variables, and long-term neurobehavioral outcome. No significant cognitive declines or worsening of depression scores were observed through the blinded phase or in open-label at 7 years. Higher scores were observed at 7 years on measures of executive functions and attention. Depression and memory-related AEs were not associated with reliable change on objective measures or 7-year neurobehavioral outcome. The AEs were without significant impact on QOL. Memory and depression AEs were not related to demographic or seizure characteristics, change in seizure frequency, frequency of AE or depression report. The authors concluded that bilateral ANT DBS was associated with subjective depression and memory AEs during the blinded phase in a minority of patients that were not accompanied by objective, long-term neurobehavioral worsening. Monitoring and neuropsychological assessment of depression and memory are recommended from a theoretical stand-point and because more memory and depression AEs occurred in the active stimulation than control group.

Salanova (2018) stated that the safety and efficacy DBS of the anterior nucleus of the thalamus (ANT) for epilepsy (SANTE) trial was demonstrated by a randomized trial by Fisher et al (2010). Based on this trial, the FDA granted approval for DBS therapy for epilepsy; the indication is as follows: "Bilateral stimulation of the ANT for epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial onset seizures with or without secondary generalization that are refractory to 3 or more antiepileptic medications".

Koeppen and colleagues (2019) DBS of the ANT is an adjunctive therapy for pharmaco-resistant epilepsy. To define the most efficient target in DBS for epilepsy, these investigators examined clinical data, position of leads, usability of atlas data compared to electric field modeling based on programming parameters. Data from 10 consecutive patients who underwent ANT-DBS were analyzed. The mammillo-thalamic tract (MTT), an internal landmark for direct stereotactic targeting, was segmented from MRI. Centers of stimulation were determined and their positions relative to ventricles and the MTT were analyzed; two 3-D thalamus atlases were transformed to segmented patient's thalami and proportions of activated nuclei were calculated. The data indicated higher response

rates with a center of stimulation 5 mm lateral to the wall of the 3rd ventricle (R2 for reduction of focal seizure frequency and distance to the wall of the 3rd ventricle = 0.48, p = 0.026). For reduction of focal seizures, a strong positive correlation with the dorsal distance to the mid-commissural plane was found (R2 = 0.66, p = 0.004). In one 3-D atlas, stimulation of internal medullary lamina (IML) correlated strongly positive with response rates, which, however, did not reach statistical significance (R2 = 0.69, p = 0.17 for tonic-clonic seizures). All electrical fields covered the diameter of the MTT. The position of the MTT in the thalamus was highly variable (range: x-coordinate 4.0 to 7.3 mm, y-coordinate -1.3 to 5.1 mm in AC-PC space). The authors concluded that the distance of the active contact to the lateral wall of the 3rd ventricle, MTT and the ventro-dorsal distance to mid-commissural plane appeared to be relevant for optimal target planning. For reduction of focal seizure frequency, these investigators found best response rates with a center of stimulation 5 mm lateral to the wall of the 3rd ventricle, and a lead tip 10 mm dorsal of the mid-commissural plane.

Yan and co-workers (2018) presented the first systematic review aimed at understanding the safety and efficacy of DBS for DRE in pediatric populations, emphasizing patient selection, device placement and programming, and seizure outcomes. The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations. Relevant articles were identified from 3 electronic databases (Medline, Embase, and Cochrane CENTRAL) from their inception to November 17, 2017. Inclusion criteria of individual studies were: diagnosis of DRE; treatment with DBS; inclusion of at least 1 pediatric patient (age less than or equal to 18 years); and patient-specific data. Exclusion criteria for the systematic review included missing data for age, DBS target, or seizure freedom; non-human subjects; and editorials, abstracts, review articles, and dissertations. This review identified 21 studies and 40 unique pediatric patients (aged 4 to 18 years) who received DBS treatment for epilepsy. There were 18 patients with electrodes placed in the bilateral or unilateral centro-median nucleus of the thalamus (CM) electrodes, 8 patients with bilateral ATN electrodes, 5 patients with bilateral and unilateral hippocampal electrodes, 3 patients with bilateral STN and 1 patient with unilateral STN electrodes, 2 patients with bilateral posteromedial hypothalamus electrodes, 2 patients with unilateral MTT electrodes,

and 1 patient with caudal zona incerta electrode placement. Overall, 5 of the 40 (12.5%) patients had an International League Against Epilepsy class I (i.e., seizure-free) outcome, and 34 of the 40 (85%) patients had seizure reduction with DBS stimulation. The authors concluded that DBS is an alternative or adjuvant treatment for children with DRE. Moreover, these researchers stated that prospective registries and future clinical trials are needed to identify the optimal DBS target, although favorable outcomes are reported with both CM and ATN in children.

Parkinson's Disease-Related Restless Legs Syndrome

Klepitskaya and colleagues (2018) examined the effect of STN-DBS in patients with PD and moderate-to-severe restless legs syndrome (RLS) on their RLS symptoms. Patients undergoing STN-DBS surgery for PD completed the International RLS Study Group Rating Scale (IRLS) and RLS QoL questionnaires pre-operatively and post-operatively at 6 months, 1 year, and 2 years. The primary outcome measure was IRLS sum score and subscales (severity and impact) and the secondary measure was RLS QoL scores. Differences among the mean scores over time were analyzed using mixed model regression. A total of 22 patients were enrolled. The pre-operative IRLS sum scores were 19.59 ± 6.95, severity subscale 12.91 ± 4.33, impact subscale 4.45 ± 2.72, and transformed RLS QoL score 68.30 ± 20.26. The differences between pre-operative and averaged post-operative scores were IRLS sum score -7.80, severity subscale -5.50, impact subscale -1.20, and RLS QoL 4.73. The overall F tests demonstrated differences among the times for the means of the IRLS sum and subscales: $p < 0.05$. There were no correlations between RLS symptoms improvement and PD motor symptoms improvement or reduction in PD medications; half of the patients had at least 50% improvement and 27% had resolution of their RLS symptoms (IRLS = 0). The authors concluded that STN-DBS significantly decreased RLS symptoms in patients with PD despite a decrease in dopaminergic treatment. This improvement was sustained over a 2-year period. They stated that these findings suggested that DBS could be effective for treatment of RLS in patients with PD and, possibly, in severe medication-refractory idiopathic RLS as well. The study underscored the importance of further investigations and provided directions for future research to clarify the effect of DBS on RLS symptoms. Level of Evidence = IV. This was a small (n = 22); and its main drawback was the lack of a placebo control group.

Rest Tremor Progression in Early Stage Parkinson Disease

Hacker and colleagues (2018) examined if the progression of individual motor features was influenced by early DBS; a post-hoc analysis of Unified Parkinson's Disease Rating Scale-III (UPDRS-III) score (after a 7-day wash-out) was conducted from the 2-year DBS in early PD pilot trial dataset. The prospective pilot trial enrolled patients with PD aged 50 to 75 years, treated with PD medications for 6 months to 4 years, and no history of dyskinesia or other motor fluctuations, who were randomized to receive optimal drug therapy (ODT) or DBS plus ODT (DBS + ODT). At baseline and 6, 12, 18, and 24 months, all patients stopped all PD therapy for 1 week (medication and stimulation, if applicable). UPDRS-III "off" item scores were compared between the ODT and DBS + ODT groups (n = 28); items with significant between-group differences were analyzed further. UPDRS-III "off" rest tremor score change from baseline to 24 months was worse in patients receiving ODT versus DBS + ODT ($p = 0.002$). Rest tremor slopes from baseline to 24 months favored DBS + ODT both "off" and "on" therapy ($p < 0.001$, $p = 0.003$, respectively). More ODT patients developed new rest tremor in previously unaffected limbs than those receiving DBS + ODT ($p = 0.001$). The authors concluded that these findings suggested the possibility that DBS in early PD may slow rest tremor progression. These researchers stated that future investigation in a larger cohort is needed, and these findings will be tested in the FDA-approved, phase-III, pivotal, multi-center clinical trial evaluating DBS in early PD. The long-term impact of DBS is uncertain as there initially may be a lesioning effect that dissipated over time. This study provided Class II evidence that for patients with early PD, DBS may slow the progression of rest tremor.

The drawbacks of this study included its post-hoc comparisons, small sample size (n = 28), and open-label design. This single-blind UPDRS-III sub-analysis excluded rigidity, which cannot be evaluated by video-recording, and the effect of early DBS on the 2-year progression of this cardinal feature therefore remains unknown. Medication-refractory tremor is known to respond well to STN-DBS21; however, this was not assessed during the pilot trial. In addition, without an objective PD biomarker to monitor disease progression, clinical trials such as this one must utilize currently available clinical scales. For the pilot, single-blind UPDRS-III scores were assessed after a 7-day wash-out to evaluate underlying motor symptoms. While the UPDRS-III is a validated evaluation method, there is a subjective element to this

clinical assessment, and, in lieu of a biomarker, future investigations may benefit from objective data collection technology. The open-label pilot study was also vulnerable to potential placebo/lessebo effects. However, UPDRS-III videos were rated after the study concluded by an independent neurologist blinded to treatment, “on”/“off” status, and study visit chronology.

Postural Trunk Deformities

Lizarraga and Fasano (2019) noted that the effects of DBS on postural deformities are still poorly explored. These researchers carried out a systematic review on this topic in accordance with PRISMA guidelines. All 38 studies that met pre-defined eligibility criteria had high risk of bias attributed to retrospective analysis of heterogeneous populations with variable and incompletely reported demographic and clinical characteristics, definitions, outcomes, DBS indications, targets, and settings. A total of 5 patient groups were identified in the 35 studies with individual data available: parkinsonian camptocormia (n = 96): 89 patients underwent STN and 7 GPi DBS. Camptocormia was the indication in 3 patients. After DBS, camptocormia improved in 57 of 96 patients (4.3 to 100% improvement) and remained stable or worsened in 39 of 96 patients (2 to 100% worsening). Dystonic camptocormia (n = 16): All underwent GPi-DBS. They were younger and with shorter disease duration, but longer deformity duration, compared with parkinsonian camptocormia. After GPi-DBS, camptocormia improved in all patients (50 to 100% improvement). Parkinsonian Pisa syndrome (n = 14): 11 patients underwent STN-DBS for motor fluctuations whereas Pisa syndrome was the indication for pedunculopontine and GPi-DBS in 2 patients. After DBS, Pisa improved in 10 of 14 patients (33.3 to 66.7% improvement). Dystonic opisthotonus: 2 young patients remarkably responded to GPi-DBS. Parkinsonian anterocollis: There were variable responses in 3 patients after STN-DBS for motor fluctuations. The authors concluded that low-quality level of evidence suggested that dystonic camptocormia and opisthotonus improved following GPi-DBS. Parkinsonian camptocormia, Pisa syndrome, and anterocollis had variable responses, and their dystonic features should be further examined.

Tinnitus

Sancar (2019) stated that neuromodulation using DBS showed promise in treating patients with refractory tinnitus, according to a small phase-I clinical trial. The trial enrolled 6 subjects who had severe tinnitus lasting longer than a year but didn't respond to conventional sound or behavioral therapy or both. Deep brain stimulation leads were implanted bilaterally in subjects' caudate nucleus. It took the researchers 5 to 13 months to determine the optimal electrical stimulation parameters for each patient. Afterward, 5 patients received 24 weeks of continuous DBS. At the conclusion of the study, 3 of 5 patients had a significant decrease in their Tinnitus Functional Index (TFI) score, which measures tinnitus intrusiveness, cognitive interference, sleep disturbance, auditory and relaxation issues, QOL, and emotional distress. Patients' TFI scores decreased about 23 points on average; a 13-point or greater change was considered clinically meaningful; 4 of 5 patients had clinically significant improvements in their Tinnitus Handicap Inventory (THI) score, a self-reported measure of tinnitus' effect on daily living. Subjects' mean reduction in their THI score was about 31 points; a 20-point or greater change was clinically significant. Only 1 serious AE occurred -- a suicide attempt unrelated to treatment. Other AEs included post-operative incision pain, headache, and transient worsening of tinnitus. Treatment with DBS caused no significant hearing or neuropsychiatric harm. This trial succeeded in translating incidental clinical findings into "the first ever prospective phase 1 trial of DBS in patients with tinnitus", noted an accompanying editorial, adding that a larger phase-II clinical trial could help investigators fine-tune the stimulation settings to improve outcomes.

Obsessive-Compulsive Disorder

Pallanti et al (2004) stated that more results are needed before the effectiveness of non-pharmacologic treatments (e.g., DBS) for obsessive-compulsive disorder (OCD) can be determined. Deep brain stimulation has also been examined for the treatment of epilepsy, chronic cluster headache, and Tourette syndrome (TS). However, there is currently insufficient evidence to support its effectiveness of these indications.

Raviv and colleagues (2020) carried out a systematic literature review using the PubMed database and a patient/problem, intervention, comparison, outcome search with the terms "DBS" and "OCD". Of the

86 eligible articles that underwent full-text review, 28 were included for review. Articles were excluded if the target was not specified, the focus on non-clinical outcomes, the follow-up period shorter than 3 months, or the sample size smaller than 3 subjects. Level of evidence was assigned according to the American Association of Neurological Surgeons/Congress of Neurological Surgeons joint guideline committee recommendations. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Selected publications included 9 RCTs, 1 cohort study, 1 case-control study, 1 cross-sectional study, and 16 case-series studies. Striatal region targets such as the anterior limb of the internal capsule, ventral capsule/ventral striatum, and nucleus accumbens were identified, but stereotactic coordinates were similar despite differing structural names. Only 15 of 28 articles included coordinates. The authors concluded that It has been 10 years since DBS for OCD received approval for a HDE. Despite numerous studied targets, the response to treatment is variable and likely attributable to phenotypic diversity within the psychiatric diagnosis. Given the heterogeneity in diagnosis and treatment, it is not possible to conclusively propose an ideal target that would benefit each individual patient. As such, future work should focus on individualizing therapy with respect to patient- or disease-specific factors. Patient-specific anatomy may be relevant in certain OCD subtypes, and certain striatal regions may be more effective targets; however, labeling remains inconsistent, and these researchers suggested using a common nomenclature for striatal stimulation with the reporting of active contacts relative to stereotactic coordinates.

The authors stated that this study had several drawbacks. Although the benefits of DBS include its partial reversibility and adjustable nature, it is important to recognize that there are specific risks with therapy. DBS surgery requires the chronic implantation of hardware, including the need for future generator replacements. Complications have been reported in up to 20% of cases. Furthermore, novel indications may be associated with unique or unknown risks; and require specialized centers that have expertise in implantation and programming. As such, surgery requires a detailed understanding of potential risks and a close therapeutic relationship.

In a systematic review, Mar-Barrutia and colleagues (2021) examined the existing knowledge on the effectiveness and tolerability of DBS in treatment-resistant OCD. These investigators carried out a comprehensive search in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020, using the following strategy: "(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)". Clinical trials and observational studies published in English and evaluating the effectiveness of DBS for OCD in humans were included and screened for relevant information using a standardized collection tool. The inclusion criteria were as follows: a main diagnosis of OCD, DBS conducted for therapeutic purposes and variation in symptoms of OCD measured by the Y-BOCS as primary outcome. Data were analyzed with descriptive statistics. A total of 40 articles identified by the search strategy met the eligibility criteria. Applying a follow-up threshold of 36 months, 29 studies (with 230 patients) provided information on short-term (ST) response to DBS in, while 11 (with 155 patients) reported results on long-term (LT) response. Mean follow-up period was 18.5 ± 8.0 months for the ST studies and 63.7 ± 20.7 months for the LT studies. Overall, the percentage of reduction in Y-BOCS scores was similar in ST (47.4 %) and LT responses (47.2 %) to DBS, but more patients in the LT reports met the criteria for response (defined as a reduction in Y-BOCS scores greater than 35 %: ST, 60.6 % versus LT, 70.7 %). According to the results, the response in the 1st year predicted the extent to which an OCD patient will benefit from DBS, since the maximum symptom reduction was achieved in most responders in the first 12 to 14 months after implantation. Reports indicated a consistent tendency for this early improvement to be maintained to the mid-term for most patients; but it is still controversial whether this improvement persists, increases or decreases in the long-term. Three different patterns of LT response emerged from the analysis: 49.5 % of patients had good and sustained response to DBS, 26.6 % were non-responders, and 22.5 % were partial-responders, who might improve at some point but experienced relapses during follow-up. A significant improvement in depressive symptoms and global functionality was observed in most studies, usually (although not always) in parallel with an improvement in obsessive symptoms. Most adverse effects of DBS were mild and transient and improved after adjusting stimulation parameters; however, some severe AEs including intra-cranial hemorrhages (ICHs) and infections were also described. Hypomania was the most frequently reported psychiatric side effect.

The relationship between DBS and suicide risk is still controversial and requires further study. Finally, to-date, no clear clinical or biological predictors of response can be established, probably because of the differences between studies in terms of the neuroanatomical targets and stimulation protocols assessed. The authors concluded that the present review confirmed that DBS is a promising treatment for patients with refractory, severe OCD, providing both ST and LT evidence of effectiveness.

The authors noted that this review had several drawbacks. First, these investigators decided not to restrict their search to RCTs and included open studies, series, and published clinical cases, which represented 79 % of ST studies and 91 % of LT studies. Although this made these results more representative, it also limited their methodological validity because they were unable to adequately control for biases and for the risk of a placebo response. Second, the marked heterogeneity among the studies reviewed, including sample size, study design, stimulation parameters, anatomical targets, and psychometric tools for defining primary and secondary outcomes, also made any meaningful comparison difficult. Third, many groups used other therapeutic approaches (e.g., cognitive behavioral therapy) concurrently with DBS or do not define whether pharmacological treatments were interrupted after DBS implantation; thus, these researchers could not be sure that the beneficial effects attributed to DBS were not in fact due to a multi-modal treatment approach.

Mosley, et al. (2021) reported on a randomized controlled trial of deep brain stimulation in persons with refractory obsessive compulsive disorder. Nine participants (four females, mean age 47.9 ± 10.7 years) were implanted with DBS electrodes bilaterally in the bed nucleus of the stria terminalis (BNST). Following a one-month postoperative recovery phase, participants entered a three-month randomized, double-blind, sham-controlled phase before a twelve-month period of open-label stimulation incorporating a course of cognitive behavioral therapy (CBT). The primary outcome measure was OCD symptoms as rated with the Yale-Brown Obsessive-Compulsive Scale (YBOCS). In the blinded phase, there was a significant benefit of active stimulation over sham ($p = 0.025$, mean difference 4.9 points). After the open phase, the mean reduction in YBOCS was 16.6 ± 1.9 points ($\chi 2$ (11) = 39.8, $p = 3.8 \times 10\text{-}5$), with seven participants classified as responders. CBT resulted in an additive YBOCS reduction of 4.8 ± 3.9 points ($p =$

0.011). There were two serious adverse events related to the DBS device, the most severe of which was an infection during the open phase necessitating device explantation. There were no serious psychiatric adverse events related to stimulation.

Knebel et al (2024) noted that in the search for effective treatments for refractory OCD, DBS serves as an alternative option for those with minimal response to pharmacotherapy. The rarity of reports regarding the use of DBS for the treatment of OCD is attributed to the invasive nature of the procedure: placement of electrodes within targeted areas of the brain to provide neuromodulation. This last resort approach may decrease functional impairment and pharmacologic complications for OCD. In a retrospective, single-center, case-cohort study, these researchers compared the pharmacotherapy utilization and treatment outcomes of 5 treatment-refractory OCD patients following the placement of DBS with those of a matched cohort. These investigators reviewed the electronic medical records of 5 subjects treated with DBS for refractory OCD and compared them to a similar treatment-refractory cohort whose OCD was treated without the use of DBS. Control subjects were matched by age, sex, years since diagnosis, number of previous medication class trials, as well as additional clinical factors. Inclusion criteria were age of at least 18 years, primary diagnosis of OCD according to the ICD-10 classification, and DBS treatment for refractory OCD. Exclusion criteria included co-morbid psychotic disorders, unstable neurological or coagulation disorder(s), and/or an eating disorder diagnosis. The primary endpoint was the change in the number of psychotropic medications 2 years after implantation for the DBS cohort; and 2 years after psychiatric decompensation for the comparator cohort. Secondary endpoints included: Y-BOCS changes over time, duration quantity of psychotropic medication classes prescribed, and additional symptomology scale changes. Patients receiving DBS were more likely to be on fewer medications and trialed fewer medications following treatment; 1 out of the 5 patients was found to be a responder in Y-BOCS scoring after DBS treatment. A reduction in anxiety and depression symptoms was also observed in the HAM-A and HAM-D scales for those who received DBS. The authors concluded that a reduction in psychiatric medications trialed during therapy was observed, as well as varying reductions in OCD, anxiety, and depression symptomology after DBS. These investigators stated that findings from this study showed that DBS implantation may contribute to a reduction in poly-pharmacy while displaying DBS's

potential impact on co-morbid anxiety and depression symptoms. Moreover, these researchers stated that given that the small sample size of this trial limited generalizability, additional prospective, randomized studies comparing the effectiveness of DBS for OCD-specific symptomology and its overall impact on pharmacotherapy are needed to further establish the role of DBS as an accepted therapeutic option for patients with refractory OCD.

The authors stated that drawbacks of this study included its retrospective design and small sample size (n = 5), which limited the applicability of controlled treatment environments and assessment of global treatment trends. In addition, participants had psychotherapy and medication adjustments throughout treatment in addition to their DBS setting adjustments. The combination of psychotherapy, pharmacotherapy, and other therapies remains the standard of care (SOC), especially in those with severe OCD; thus, changes in medication usage and OCD severity could not necessarily be attributed to DBS alone, and the overall small sample size limited the generalizability of the results. The absence of Y-BOCS, HAM-A, and HAM-D scores limited the ability to compare the 2 groups in terms of therapeutic effectiveness outside of pharmacotherapy comparisons. Given the severity/treatment-refractory diagnosis of OCD in the studied patients, the impact of pharmacotherapy and psychotherapy may be limited. The cohorts were also not matched according to ethnicity, which introduced another confounding variable as cultural factors have been shown to influence the expression and perception in the treatment of severe mental illness. Race, spirituality, and country of origin were a few of these cultural factors that could have influenced treatment response. Limited symptomology data for the comparator cohort and missing data for 1 patient who received DBS treatment also limited comparison of Y-BOCS scores across groups.

Brain Magnetic Resonance Imaging (MRI) for Pre-Operative Planning or Intra-Operative Navigation for Implantation of Deep Brain Stimulator

Alterman et al (1999) examined the accuracy of targeting nucleus ventralis intermedius (Vim) with fast spin echo inversion recovery (FSE/IR) magnetic resonance imaging (MRI) in 18 successful deep brain stimulator (DBS) implants for medically refractory tremor. FSE/IR-MRI-derived coordinates were compared to the final coordinates employed for DBS lead placement, selected with intra-operative

neurophysiology. The authors concluded that FSE/IR MRI was sufficiently reliable to serve as the sole means of anatomically targeting Vim for DBS lead placement. An independent computer work-station was not required for accurate targeting; however, intra-operative neurophysiology remains essential.

Kovacs et al (2006) stated that there is a great need for MRI examinations of patients who have previously undergone DBS implantation. The current guidelines pertain only to a 1.5-Tesla horizontal-bore scanner complying with strict safety regulations. Moreover, almost all published in-vitro and in-vivo studies concerning patient safety were carried out on 1.5 Tesla MR scanners. These researchers shared their clinical experience of 1.0-Tesla brain MR imaging. During the past 4 years, 34 patients with different types of implanted DBS systems underwent 1.0-Tesla MR examinations to answer diagnostic or clinical questions. Apart from the scanner type applied, all other safety instructions were strictly followed. The MRI itself made no significant difference to the measured impedances or the stimulation parameters needed to achieve the optimal therapeutic results. From theoretical considerations, it may be assumed that 1.0-Tesla MRI could be performed safely on DBS-implanted patients, provided that all other recommendations were adhered to.

Giller et al (2012) stated that centers implanting DBS electrodes on different days often protect the 1st electrode tip with a protective cap, tunneled it under the scalp, and connected it to the generator at a later procedure. If MRI is used for planning during the 2nd implantation, MRI artifacts from the protective cap could potentially corrupt the stereotactic coordinates. The importance of this problem may increase if emerging MRI safety data led to more frequent use of MRI for these purposes. These researchers described an MRI artifact arising from the use of the standard protective DBS cap that corrupted stereotactic planning and described a way to avoid the artifact. After noting the artifact during a staged DBS procedure, a non-metallic silastic sleeve contained in the existing DBS implantation kit was used in 9 subsequent patients. Two caps with standard metallic screws were also tested with MRI phantoms. The silastic sleeve protected the DBS electrode but did not produce MRI artifact. The phantom studies demonstrated significant artifact from caps containing screws. The

authors concluded that a silastic sleeve provided adequate protection of the DBS electrode during staged implantation and avoided the MRI artifact associated with protective caps with screws.

Martin et al (2017a) examined the incidence of post-operative hardware infection following intraoperative MRI (iMRI)-guided implantation of DBS electrodes in a diagnostic MRI scanner. A diagnostic 1.5-T MRI scanner was used over a 10-year period to implant DBS electrodes for movement disorders. The MRI suite did not meet operating room standards with respect to airflow and air filtration but was prepared and used with conventional sterile procedures by an experienced surgical team. Deep brain stimulation leads were implanted while the patient was in the magnet, and patients returned 1 to 3 weeks later to undergo placement of the implantable pulse generator (IPG) and extender wire in a conventional operating room. Surgical site infections requiring the removal of part or all of the DBS system within 6 months of implantation were scored as post-operative hardware infections in a prospective data-base. During the 10-year study period, the authors performed 164 iMRI-guided surgical procedures in which 272 electrodes were implanted. Patients ranged in age from 7 to 78 years, and an overall infection rate of 3.6% was found. Bacterial cultures indicated Staphylococcus epidermis (3 cases), methicillin-susceptible Staphylococcus aureus (2 cases), or Propionibacterium sp. (1 case). A change in sterile practice occurred after the first 10 patients, leading to a reduction in the infection rate to 2.6% (4 cases in 154 procedures) over the remainder of the procedures. Of the 4 infections in this patient subset, all occurred at the IPG site. The authors concluded that iMRI-guided DBS implantation can be performed in a diagnostic MRI suite with an infection risk comparable to that reported for traditional surgical placement techniques provided that sterile procedures, similar to those used in a regular operating room, were practiced.

Martin et al (2017b) stated that iMRI is increasingly used to implant DBS electrodes. The approach has the advantages of a high targeting accuracy, minimization of brain penetrations, and allowance of implantation under general anesthesia. The hemorrhagic complications of iMRI-guided DBS implantation have not been studied in a large series. These investigators reported on the incidence and characteristics of hemorrhage during these procedures. Hemorrhage incidence was assessed in a series of 231 iMRI procedures (374

electrodes implanted). All patients had movement disorders and the subthalamic nucleus or the globus pallidus internus was typically targeted. Hemorrhage was detected with intra- or post-operative MRI or post-operative computed tomography (CT). Hemorrhage was classified based on its point of origin and clinical impact. Hemorrhage and symptomatic hemorrhage were detected during 2.4 and 1.1% of electrode implantations, respectively. The hemorrhage origin was subdural/subarachnoid (n = 3), subcortical (n = 5), or deep (n = 1). Factors that contributed to hemorrhage included un-intentional crossing of a sulcus and resistance at the pial membrane, which produced cortical depression and a rebound hemorrhage. Delayed hemorrhage occurred in 2 patients and was attributed to premature re-introduction of anti-coagulation therapy or air intrusion into the cranial cavity. The authors concluded that hemorrhage was readily apparent on intra-operative imaging, and hemorrhage rates for iMRI-guided DBS implantations were comparable to those for conventional implantation approaches.

Huntington's Disease

Bonomo and colleagues (2021) stated that HD is a neurodegenerative disorder characterized by involuntary movements, cognitive decline, and behavioral changes. The complex constellation of clinical symptoms still makes the therapeutic management challenging. In the new era of functional neurosurgery, DBS may represent a promising therapeutic approach in selected HD patients. In a systematic review, articles describing the effect of DBS in patients affected by HD were selected from Medline and PubMed by the association of text words with MeSH terms as follows: "Deep brain stimulation", "DBS", and "HD", "Huntington's disease", and "Huntington". Details on repeat expansion, age at operation, target of operation, duration of follow-up, stimulation parameters, AEs, and outcome measures were collected. A total of 20 eligible studies, assessing 42 patients with HD, were identified. The effect of globus pallidus internus (GPi) DBS on Unified Huntington's Disease Rating Scale (UHDRS) total score revealed in 10 studies an improvement of total score from 5.4 % to 34.5 %, and in 4 studies, an increase of motor score from 3.8 % to 97.8 %. Bilateral GPi-DBS was reported to be effective in reducing Chorea sub-score in all studies, with a mean percentage reduction from 21.4 % to 73.6 %. The authors concluded that HD patients with predominant choreic symptoms may be the best candidates for surgery; however, the role of other clinical features and of disease progression should be

elucidated. For this reason, there is a need for more reliable criteria that may guide the selection of HD patients suitable for DBS. Accordingly, further studies including functional outcomes as primary endpoints are needed.

Obesity

Lopez and colleagues (2022) stated that obesity has become a major public health concern worldwide, with current behavioral, pharmacological, and surgical treatments offering varying rates of success and adverse effects. Neurosurgical approaches to treatment of refractory obesity include DBS on either specific hypothalamic or reward circuitry nuclei, which might contribute to weight reduction via different mechanisms. In a systematic review, these investigators examined the safety and clinical effect of DBS in medical refractory obesity. Adhering to PRISMA guidelines, these researchers identified all original studies -- observational and experimental -- in which DBS was carried out for the treatment of refractory obesity. From database inception to April 2021, these investigators performed their searches in PubMed, Scopus, and LILACS databases using the following MeSH terms: "Obesity" OR "Prader-Willi Syndrome" AND "Deep Brain Stimulation". The main outcomes were safety and weight loss measured with the BMI. The GRADE methods were used to examine the quality of evidence. A total of 7 studies involving 12 patients met the inclusion criteria; the DBS target was the nucleus accumbens in 4 (57.1 %), the lateral hypothalamic area in 2 (29.6 %), and the ventral hypothalamus in 1 (14.3 %). Furthermore, 33 % of subjects had obesity secondary to Prader-Willi syndrome (PWS) and 66.6 % had primary obesity. The global BMI average at baseline was 46.7 (SD: 9.6, range of 32.2 to 59.1), and after DBS, 42.8 (SD: 8.8, range of 25 to 53.9), with a MD of 3.9; however, the delta in PWS patients was -2.3 and 10 in those with primary obesity. The incidence of moderate side effects was 33 % and included manic symptoms (n = 2), electrode fracture (n = 1), and seizure (n = 1); mild complications (41.6 %) included skin infection (n = 2), difficulties falling asleep (n = 1), nausea (n = 1), and anxiety (n = 1). The authors concluded that despite available small case series and case reports reporting a benefit in the treatment of refractory obesity with DBS, this systematic review emphasized the need for prospective studies with longer follow-ups in order to further address the effectiveness and indications.

Chorea-Acanthocytosis

Richard and associates (2019) stated that chorea-acanthocytosis (ChAc) is a rare autosomal recessive neurodegenerative disease due to mutation of the VPS13A gene encoding the protein chorein. ChAc is a slowly progressive disorder that typically presents in early adulthood, and whose clinical features include chorea and dystonia with involuntary lip, cheek, and tongue biting. Some patients also have seizures. Treatment for ChAc is symptomatic. A small number of ChAc patients have been treated with bilateral DBS of the globus pallidus interna (GPi); these investigators presented an additional case. Patient chart, functional measures, and laboratory findings were reviewed from the time of ChAc diagnosis until 6 months after DBS surgery. The authors described a case of ChAc in a 31-year-old man positive for VPS13A gene mutations who presented with chorea, tongue biting, dysarthria, weight loss, and mild cognitive dysfunction. DBS using monopolar stimulation with placement slightly lateral to the GPi was associated with significant improvement in chorea and dysarthria. This case added to the current state of knowledge regarding the safety and effectiveness of bilateral GPi-DBS for symptomatic control of drug-resistant hyperkinetic movements seen in ChAc. Moreover, these researchers stated that controlled trials are needed to better evaluate the impact and ideal target of DBS in ChAc. They stated that the main drawback of this study was its open-label nature of the treatment. The excellent clinical outcome in the setting of lead placement lateral to the GPi raised questions as to the optimal target in patients with ChAc.

Wu and colleagues (2022) noted that DBS is a reversible treatment for ChAc; however, its safety and effectiveness remain elusive due to the low prevalence of ChAc. In a systematic review, these investigators examined the safety and effectiveness of DBS for ChAc by examining literature through PubMed and Embase. Inclusion criteria were reports on the safety or effectiveness of DBS for ChAc and English language articles, and exclusion criteria were other movement disorders, non-human subjects, and studies without original data. Most studies were published as case reports; thus, these researchers pooled these cases in one cohort. A total of 20 studies with 34 patients were included. The mean age of symptom onset was 29.3 years (range of 17 to 48). The median follow-up was 12 months (range of 2 to 84); 29 patients underwent GPi-DBS, 2 received STN-DBS, and 1 underwent Vop-DBS. Electrodes were implanted into the ventralis oralis complex of

the thalamus and the pallidal in 2 patients. Symptoms appeared to be easier relieved in chorea (88.5 %) and dystonia (76.9 %) but dysarthria of most patients (85.7 %) was no response after DBS. The UHDRS-Motor Score was used to evaluate the effectiveness of DBS in 25 patients; the mean score decreased from 43.2 to 22.3 and the median improvement rate was 46.7 %. Of 24 patients with data on AEs, complications occurred in 9 patients (37.5 %; mostly transient and mild events). The authors concluded that DBS is a promising treatment for ChAc with satisfactory safety and effectiveness based on the review. Pallidal and thalamic DBS have been used in ChAc; GPi-DBS appeared to be more widely used.

Furthermore, an UpToDate review on “Neuroacanthocytosis” (Ralph, 2021) states that “Deep brain stimulation and other neurosurgical procedures have been tried in a handful of cases. In one individual, bilateral thalamic brain stimulation did significantly reduce trunk spasms, and the benefit lasted for 1 year. Bilateral stimulation of the globus pallidus interna has been helpful in some cases, but not in others”.

Alzheimer's Disease

Cheyuo et al (2022) stated that DBS and non-invasive neuromodulation are currently being examined for treating network dysfunction in Alzheimer's Disease (AD). However, due to heterogeneity in techniques and targets, the cognitive outcome and brain network connectivity remain unknown. These investigators carried out a systematic review, meta-analysis, and normative functional connectivity to determine the cognitive outcome and brain networks of DBS and non-invasive neuromodulation in AD. PubMed, Embase, and Web of Science were searched using 3 concepts: dementia, brain connectome, and brain stimulation, with filters for English, human studies, and publication dates 1980 to 2021. Additional records from clinicaltrials.gov were added. Inclusion criteria were AD study with DBS or non-invasive neuromodulation and a cognitive outcome. Exclusion criteria were less than 3-months follow-up, severe dementia, and focused ultrasound (US) intervention. Bias was evaluated using Centre for Evidence-Based Medicine levels of evidence. These researchers performed meta-analysis, with subgroup analysis based on type and age at neuromodulation. To determine the patterns of neuromodulation-induced brain network activation, they conducted normative functional connectivity using resting-state

functional MRI (rsfMRI) of 1,000 healthy subjects. A total of 6 studies, with 242 AD patients, met inclusion criteria. On fixed-effect meta-analysis, non-invasive neuromodulation favored baseline, with effect size -0.40 (95 % CI: -0.73 to -0.06, p = 0.02), while that of DBS was 0.11 (95 % CI: -0.34 to 0.56, p = 0.63), in favor of DBS. In patients 65 years of age or older, DBS improved cognitive outcome, 0.95 (95 % CI: 0.31 to 1.58, p = 0.004), whereas in patients less than 65 years of age baseline was favored, -0.17 (95 % CI: -0.93 to 0.58, p = 0.65). Functional connectivity regions were in the default mode (DMN), salience (SN), central executive (CEN) networks, and Papez circuit. The subgenual cingulate and anterior limb of internal capsule (ALIC) showed connectivity to all targets of neuromodulation. The authors concluded that this meta-analysis provided level II evidence of a difference in response of AD patients to DBS, based on age at intervention. Brain stimulation in AD may modulate DMN, SN, CEN, and Papez circuit, with the subgenual cingulate and ALIC as good targets for future DBS trials in AD.

Karaszewska et al (2022) noted that several pioneering studies examined DBS in treatment-refractory AN patients; however, overall effects remain yet unclear. In a systematic review and meta-analysis, these researchers obtained estimates of effectiveness of DBS in AN-patients. These investigators examined 3 electronic databases until November 1, 2021, using terms related to DBS and AN. They included studies that examined the clinical effects of DBS in AN-patients. These researchers obtained data including psychiatric co-morbidities, medication use, DBS target, and study duration. Primary outcome was BMI, secondary outcome was QoL, and the severity of psychiatric symptoms, including eating disorder, obsessive-compulsive, depressive, and anxiety symptoms. They assessed the risk of bias using the ROBINS-I tool. A total of 4 studies were included for meta-analysis, with a total of 56 patients with treatment-refractory AN. Follow-up ranged from 6 to 24 months. Random effects meta-analysis showed a significant increase in BMI following DBS, with a large effect size (Hedges's g = 1 · 13; 95 % CI: 0.80 to 1.46; Z-value = 6.75; p < 0.001), without heterogeneity (I2 = 0.00, p = 0.901). Random effects meta-analysis also showed a significant increase in QoL (Hedges's g = 0.86; 95 % CI: 0.44 to 1.28; Z-value = 4.01, p < 0.001). Furthermore, DBS decreased the severity of psychiatric symptoms (Hedges's g = 0.89; 95 % CI: 0.57 to 1.21; Z-value = 5.47; p < 0.001, I2 = 4.29, p = 0.371). The authors concluded that in this 1st meta-analysis, DBS

showed statistically large beneficial effects on weight restoration, QoL, and reduction of psychiatric symptoms in patients with treatment-refractory AN. These outcomes call for more extensive naturalistic studies to determine the clinical relevance for functional recovery.

Yan et al (2024) examined the control effect of DBS on AD from a neuro-computational perspective. First, a data-driven cortical network model was constructed using diffusion tensor imaging (DTI) data. Then, a typical electrophysiological feature of EEG slowing in AD was reproduced by reducing the synaptic connectivity parameters. The corresponding changes in kinetic behavior mainly include an oscillation decrease in the amplitude and frequency of the pyramidal neuron population. Subsequently, DBS current with specific parameters was introduced into 3 potential targets -- the hippocampus, the nucleus accumbens, and the olfactory tubercle, respectively. The results showed that applying DBS to simulated mild AD patients induced an increase in relative alpha power, a decrease in relative theta power, and a significant right-ward shift of the dominant frequency. This was consistent with the EEG reversal in pharmacotherapies for AD. In addition, the optimal stimulation strategy of DBS was examined via spectral and statistical analyses. Specifically, the pathological symptoms of AD could be alleviated by adjusting the critical parameters of DBS, and the control effect of DBS on various targets was that the hippocampus was superior to the olfactory tubercle and nucleus accumbens. Lastly, by means of correlation analysis between the power increments and the nodal degrees, it was concluded that the control effect of DBS was related to the importance of the nodes in the brain network. The authors concluded that the findings of this study provided a theoretical guidance for determining DBS targets and parameters, which may have a substantial impact on the development of DBS for the treatment of patients with AD.

Anorexia Nervosa

Hsu et al (2022) stated that anorexia nervosa (AN) and obesity are common appetite disorders, which may be life-threatening if not treated and often coincide with psychiatric disorders. In a systematic review, these investigators examined if DBS of specific regions within the brain could aid in treating these disorders. They organized the literature regarding the feasibility of DBS via clinical outcomes and synthesize the data on patient demographics and electrode parameters for future optimization. PubMed, Scopus, and Web of Science databases were

all queried on June 7, 2022 to identify studies reporting the effect of DBS in treatment of either AN or obesity. These researchers included studies involving DBS; treatment of AN or obesity, and BMI as the primary outcome variable. Case-reports, retrospective cohort studies, and RCTs were all eligible for inclusion. Exclusion of articles was based on the either of the following 2 criteria: Meta-analyses or systematic reviews or describes diseases other than only AN or obesity. Screening of the 999 articles returned by an initial search yielded 23 studies for inclusion and further data extraction. Qualitative assessment of included studies was subsequently conducted in accordance with Newcastle-Ottawa Scale criteria. This review included 23 articles (17 AN, 5 obesity) that met the inclusion and exclusion criteria, which included 8 case-reports, 13 case-series study, and 1 case-control study. The primary variables of interest were location of DBS, change in BMI after intervention, electrode parameters, and psychiatric co-morbidities. A total of 131 patients were included and analyzed, 118 of those belonging in the AN cohort. For patients with AN, these investigators found that the most common place for DBS was the subcallosal cingulate followed by the nucleus accumbens (NA), resulting in an overall increase in BMI by 24.82 % over the span of a mean 17.1 months. Psychiatric co-morbidities (MDD, OCD, and anxiety) were common in the AN cohort. For patients with obesity, DBS was most common in the lateral hypothalamus followed by the NA, resulting in a small decrease in BMI by 3.97 % over a mean 17.2 months. Data were insufficient for this cohort to report on additional psychiatric co-morbidities or calculate the duration from diagnosis to treatment. The authors concluded that DBS appeared to be a promising solution in addressing treatment-refractory AN; however, additional prospective studies are needed to confirm this same usefulness for the treatment of obesity. Primary limitations included the apparent lack of data on DBS for obesity as well as the dearth of cohort studies evaluating the effectiveness of DBS compared with control treatments. Although these limitations could not be addressed in the current review, this study may incentivize future trials to examine DBS in patients with appetite disorders in a more controlled fashion.

Lennox-Gastaut Syndrome with Status Epilepticus

Thirunavu et al (2021) noted that Lennox-Gastaut syndrome (LGS) is a severe form of childhood onset epilepsy in which patients require multiple medications and may be candidates for palliative surgical intervention. In a meta-analysis, these researchers examined the

impact of palliative vagus nerve stimulation (VNS), corpus callosotomy (CC), and resective surgery (RS) by analyzing their impact on seizure control, anti-epileptic drug (AED) usage, QoL, behavior, cognition, prognostic factors, and complications. They carried out a systematic search of PubMed Medline, Scopus, and Cochrane Database of Systematic Reviews to find articles that met the following criteria: First, prospective/retrospective study with original data. Second, at least 1 LGS surgery patient aged less than 18 years. Third, information on seizure frequency reduction (measured as percentage, Engel class, or qualitative comment). Seizures were analyzed quantitatively in a meta-analysis of proportions and a random-effects model, whereas other outcomes were analyzed qualitatively. A total of 40 studies with 892 LGS patients met the selection criteria, with 19 reporting on CC, 17 on VNS, 4 on RS, 2 on RS + CC, 1 on CC + VNS, and 1 on DBS. CC seizure reduction rate was 74.1 % (95 % CI: 64.5 % to 83.7 %), and VNS was 54.6 % (95 % CI: 42.9 % to 66.3%), which was significantly different ($p < 0.001$). RS seizure reduction was 88.9 % (95 % CI: 66.1 % to 99.7 %). Many VNS patients reported alertness improvements, and most had no major complications. VNS was most effective for atonic/tonic seizures; higher stimulation settings correlated with better outcomes. CC patients reported moderate cognitive and QoL improvements; disconnection syndrome, transient weakness, and respiratory complications were noted. Greater callosotomy extent correlated with better outcomes. AED usage most often did not change following surgery. RS showed considerable QoL improvements for patients with localized seizure foci. In the reported literature, CC appeared to be more effective than VNS for seizure reduction. VNS may provide a similar or higher level of QoL improvement with lower aggregate risk of complications. Patient selection, anatomy, and seizure type would inform decision-making. The authors noted that given the small number of studies examining RS + CC, VNS + CC, and DBS (n = 1 study; 13 patients), these studies were not subjected to quantitative meta-analysis.

Dalic et al (2022a) stated that prior uncontrolled studies have reported seizure reductions following DBS in patients with LGS; however, evidence from RCTs is lacking. In a prospective, double-blind, randomized study, these researchers examined the safety and effectiveness of DBS to the centro-median thalamic nucleus (CM) for the treatment of LGS. Following pre- and post-implantation periods, 50 % of the subjects received 3 months of stimulation (blinded phase),

then all received 3 months of stimulation (unblinded phase). The primary outcome was the proportion of participants with 50 % or more reduction in diary-recorded seizures in stimulated versus control participants, measured at the end of the blinded phase. A secondary outcome was the proportion of participants with a 50 % or more reduction in electrographic seizures on 24-hour ambulatory EEG at the end of the blinded phase. Between November 2017 and December 2019, a total of 20 young adults with LGS (17 to 37 years;13 women) underwent bilateral CM-DBS at a single center in Australia, with 19 randomized (treatment, n = 10 and control, n = 9); 50 % of the stimulation group achieved 50 % or more seizure reduction, compared with 22 % of controls (odds ratio [OR] = 3.1, 95 % CI: 0.44 to 21.45, p = 0.25). For electrographic seizures, 59 % of the stimulation group had 50 % or more reduction at the end of the blinded phase, compared with none of the controls (OR = 23.25, 95 % CI: 1.0 to 538.4, p = 0.05). Across all patients, median seizure reduction (baseline versus study exit) was 46.7 % (inter-quartile range [IQR] = 28 % to 67 %) for diary-recorded seizures and 53.8 % (IQR = 27 % to 73 %) for electrographic seizures. The authors concluded that CM-DBS in patients with LGS reduced electrographic rather than diary-recorded seizures, after 3 months of stimulation; 50 % of all participants had diary-recorded seizures reduced by half at the study exit, providing supporting evidence of the treatment effect.

These researchers stated that much work remains in deciphering the optimal stimulation paradigms for DBS in LGS, and for patients with epilepsy more broadly. These investigators based their stimulation parameters on that of the successful SANTE study, but it was important to note that their DBS stimulation/targeting and patient cohort differed. Maximum stimulation varied between the studies (2.5 V in the ESTEL (Electrical Stimulation of Thalamus for Epilepsy of Lennox-Gastaut phenotype) Trial versus 5 to 10 V in the SANTE study) to maintain adequate blinding in the ESTEL trial. There may have been more sizeable seizure reductions observed in the ESTEL trial if higher stimulation was delivered. CM, rather than anterior thalamic nucleus (AnT), was chosen due to its widespread connections with the striatum, brainstem, and diffuse frontal areas, theoretically making it a good target for generalized epilepsies. Furthermore, the intra-operative depth electrode recordings from the beginning of tonic seizures demonstrated sustained burst firing in CM, confirming its involvement in this characteristic seizure type. However, other thalamic nuclei may

be similarly or more effective. In addition, different stimulation parameters produced specific neuronal activity patterns. These researchers stated that further investigations are needed to evaluate optimal frequency, amplitude, mode (i.e., controlled current versus voltage), and stimulation duration parameters.

Warren et al (2022) noted that DBS could reduce seizures in LGS; however, little is known regarding the optimal target and whether effectiveness would depend on connectivity of the stimulation site. Using outcome data from the ESTEL trial, these investigators determined the optimal target and connectivity for DBS in LGS. A total of 20 patients underwent bilateral DBS of the thalamic CM. Outcome was percentage seizure reduction from baseline after 3 months of DBS, defined using 3 measures (monthly seizure diaries, 24-hour scalp EEG, and a novel diary-EEG composite). Probabilistic stimulation mapping identified thalamic locations associated with higher/lower efficacy. Two substitute diffusion MRI datasets (a normative dataset from healthy subjects and a "disease-matched" dataset from a separate group of LGS patients) were used to calculate structural connectivity between DBS sites and a map of areas known to express epileptic activity in LGS, derived from the authors' previous EEG-fMRI research. Results were similar across the 3 outcome measures. Stimulation was most effective in the anterior and inferolateral "parvocellular" CM border, extending into the ventral lateral nucleus (posterior subdivision). There was a positive association between diary-EEG composite seizure reduction and connectivity to areas of a priori EEG-fMRI activation, including pre-motor and pre-frontal cortex, putamen, and pontine brainstem. In contrast, outcomes were not associated with baseline clinical variables. Effective CM-DBS for LGS was linked to stimulation of the parvocellular CM and the adjacent ventral lateral nucleus, and was associated with connectivity to, and thus likely modulation of, the "secondary epileptic network" underlying the shared electroclinical manifestations of LGS.

The authors stated that the ESTEL Trial included patients with structural brain abnormalities and previous neurosurgery including CC, which required a pragmatic analysis approach. From an imaging/connectivity perspective, it would have been preferable to exclude such patients; however, this did not represent the LGS population, where 50 % or more have structural brain abnormalities and many undergo other palliative procedures early in their clinical

journey. To circumvent this issue, these researchers modeled connectivity using normative and disease-matched substitute diffusion-weighted imaging (DWI) datasets, as in previous studies. Although the largely ipsilateral nature of thalamic connections may be protective against bias due to CC, it was possible that these findings were influenced by inclusion of patients with previous neurosurgery. The researchers stated that large, multi-center collaborations are needed to disentangle these factors, and to examine the predictive value of their findings at the individual patient level.

Dalic et al (2022b) previously reported seizure and EEG outcomes of the ESTEL Trial. To assess potential cognitive and behavioral changes during chronic, duty-cycle stimulation of bilateral thalamic CM, these researchers compared standardized cognitive and behavioral measurements, as well as caregiver assessments of disability/severity, before implantation and after 3-months stimulation. A total of 20 patients with LGS (17 to 37 years; 13 females) were studied; 1 subject was not randomized due to DBS device removal, with outcomes of 19 remaining subjects reported. Cognitive and behavioral measurements were carried out at baseline (i.e., before DBS implantation), at the end of the blinded stimulation phase, and at study exit. Instruments measured cognition (NIH toolbox cognitive battery, NIHTB-CB), adaptive skills (ABAS-3), epilepsy severity (GASE) and disability (GAD), QoL (QOLIE-31), and depression (PHQ-9). Changes in scores after 3 months of stimulation relative to baseline were explored using Wilcoxon matched-pairs signed rank tests. After 3-months of stimulation, GASE and GAD improved ($p < 0.05$). No other instrument showed a significant change from baseline. Measurements that required direct subject involvement, rather than caregivers, was completed by only a subset of higher-functioning individuals (NIHTB-CB, n = 13; QOLIE-31, n = 3; and PHQ-9, n = 6). In addition to cognitive impairments, behavioral and physical limitations were common obstacles to instrument completion. Standardized scores were hindered by “floor effects”; however, raw scores better reflected clinical impressions of subjects' functioning and were more sensitive to caregiver-reported changes following treatment. The authors concluded that DBS treatment was associated with reduced epilepsy severity and disability in young adults with LGS. Performing cognitive and behavioral outcome measurement in patients with cognitive

impairment was challenging but possible and required careful selection of instruments and modifications of score interpretation to avoid floor effects.

In a systematic review, Alanazi and Alkhani (2022) examined the available evidence regarding the safety and effectiveness of DBS in patients with LGS. These investigators carried out a systematic review of PubMed databases using keywords relevant to the objective of this research. Titles and abstracts were reviewed, after which studies that met the inclusion criteria were selected. Findings were reported according to the PRISMA guidelines. A total of 13 studies were identified, and only 3 studies that reported 50 patients (age ranged from 3 to 65 years) met the inclusion criteria of DBS for LGS. Radiological imaging findings and neurophysiological findings were described in all studies. The thalamus nuclei, particularly the CM thalamic nucleus (CMN), were found to be highly active in LGS. By targeting this brain region, patients showed favorable outcomes. Overall, the mean seizure reduction was more than 50 % in all patients (among whom 2 were seizure-free) at a mean follow-up of 15 (12 to 18) months. The authors concluded that according to this systemic review, DBS for LGS showed satisfactory outcomes, indicating that DBS should be considered a valid therapeutic option. Moreover, these researchers stated that more studies are needed to examine the role of DBS in LGS by establishing accurate targeting of the CMN using proper lead positioning and radiological imaging, a standard DBS intervention, and long-term outcomes.

Furthermore, UpToDate reviews on “Lennox-Gastaut syndrome” (Wilfong, 2022), and “Convulsive status epilepticus in adults: Management” (Drislane, 2022) do not mention DBS as a management / therapeutic option.

Chemical Dependency Disorders

Sobstyl et al (2021) stated that DBS has achieved substantial success as a treatment for movement disorders such as PD, essential tremor (ET), and dystonia. More recently, a limited number of basic and clinical studies have indicated that DBS of the NA and other neighboring structures of the reward circuit may be an effective intervention for patients with treatment-refractory addiction. These investigators carried out a structured literature review of human studies of DBS for addiction outlining the effectiveness and AEs. They

identified 14 human studies targeting mostly the NA with neighboring structures such as ALIC. A total of 5 studies including 12 patients reported the outcomes for alcohol dependence; 9 studies including 18 patients reported the outcomes for addictions to various psychoactive substances. The most common indication was addiction to heroin, found in 13 patients, followed by methamphetamine, 3 patients, cocaine, 1 patient, and polysubstance drug abuse in 1 patient. The authors concluded that the limited clinical data available indicated that DBS may be a promising therapeutic modality for the treatment of intractable addiction. In general, the safety profile of DBS in patients with addiction was good. Based on the data published in the literature, the NA is the most often targeted, and is probably the most effective, structure of the reward circuit in the treatment of addiction in humans. Moreover, these researchers stated that given the ever-expanding understanding of the psychosurgery of addiction, DBS could in the future be a therapeutic option for patients suffering from intractable addictive disorders.

Fattahi et al (2022) noted that opioid use disorder (OUD) is a chronic and complex disease characterized by repeated relapses and remissions; DBS has been examined as a potentially helpful neuro-modulatory procedure in this context. In a systematic review of pre-clinical and clinical evidence, these investigators examined the positive and negative effects of DBS in human and animal models of opioid dependence to evaluate the viability of DBS as a treatment of OUD. Eligible studies were incorporated by a comprehensive literature search and examined via proper methodological quality assessment tools. Findings showed that the NA was the most stimulated brain target in human and animal studies, and DBS was used mainly in the form of high-frequency stimulation (HFS). DBS administration effectively reduced opioid craving and consumption in human and animal subjects dependent on opioids. The authors concluded that DBS represents a valuable alternative strategy for treating intractable opioid addiction. Moreover, these researchers stated that based on this systematic literature analysis, research efforts in this field should be continued.

Chang et al (2022) noted that drug addiction is a chronic psychiatric disorder characterized by compulsive drug-seeking and drug-using behavior, and a tremendous socioeconomic burden to society. Current pharmacological and psychosocial methods have shown limited

treatment effects for substance abuse; DBS is a novel treatment for psychiatric disease and has gradually gained popularity in the treatment of addiction. Addiction is characterized by neuroplastic changes in the NA, a key structure in the brain reward system, and DBS in this region has shown promising treatment effects. These investigators reviewed the research progress on DBS for drug addiction. In particular, they discussed the mechanism of NA-DBS for addiction treatment and summarized the results of clinical trials on DBS treatment for addiction to psychoactive substances such as nicotine, alcohol, cocaine, opioids and methamphetamine/amphetamine. The authors concluded that the use of DBS treatment for drug addiction is challenging but promising. However, it should be noted that most results are obtained from case-reports. These researchers stated that further double-blinded studies and clinical trials, potential synergy with other non-invasive interventions, and larger patient populations are needed to validate DBS as a standard therapeutic option for refractory substance use disorders.

Eskandari et al (2023) stated that addiction to psychostimulants significantly affects public health. Standard medical therapy is often not curative; and (DBS is a promising treatment that has attracted much attention for addiction treatment in recent years. In a pre-clinical and clinical systematic review, these investigators examined the positive and adverse effects of DBS in human and animal models to evaluate the feasibility of DBS as a treatment for psychostimulant abuse. This review also examined the possible mechanisms underlying the therapeutic effects of DBS. In February 2022, a comprehensive search of 4 databases, including Web of Science, PubMed, Cochrane, and Scopus, was performed to identify all reports that DBS was a treatment for psychostimulant addiction . The selected studies were extracted, summarized, and evaluated using the appropriate methodological quality assessment tools . The results indicated that DBS could reduce relapse and the desire for the drug in human and animal subjects without any severe side effects. The underlying mechanisms of DBS are complex and likely vary from region to region in terms of stimulation parameters and patterns. The authors concluded that DBS appeared to be a promising therapeutic option; however, these researchers stated that clinical experiences are currently limited to several uncontrolled case reports. They noted that further studies with controlled, double-blind designs are needed. Furthermore, more research on animals and humans is needed to

examine the precise role of DBS and its mechanisms to achieve optimal stimulation parameters and develop new, less invasive methods.

Chronic Pain

Yang et al (2023) stated that chronic pain has been a major problem in personal QOL and social economy, causing psychological disorders in people and a larger amount of monetary loss in society. Some targets were adopted for chronic pain; however, the effectiveness of the centro-median (CM) nucleus for pain was still unclear. In a systematic review, these investigators examined the effectiveness of Gamma Knife (GK) surgery and DBS of the CM nucleus for the management of chronic pain. PubMed, Embase and Medline were searched to review all studies discussing GK surgery and DBS on the CM nucleus for chronic pain. Studies that were review, meet, conference, not English or not the therapy of pain were excluded. Demographic characteristics, surgery parameters and outcomes of pain relief were selected. A total of 101 patients across 12 studies were included. The median age of most patients ranged from 44.3 to 80 years when the duration of pain ranged from 5 months to 8 years. This review showed varied results of 30 % to 100 % pain reduction across studies. The difference in the effect between GK surgery and DBS could not be judged. Moreover, 3 retrospective studies related to GK surgery of the CM nucleus for trigeminal neuralgia presented an average pain relief rate of 34.6 % to 82.5 %; 4 studies reported adverse effects in a small number of patients. The authors concluded that GK surgery and DBS of the CM nucleus might be promising therapeutic approaches for chronic refractory pain. Moreover, these researchers stated that further rigorous studies with larger samples and longer follow-up durations are needed to support the safety and effectiveness of these approaches.

Movement Disorders After Stroke

Paro et al (2023) noted that stroke remains the leading cause of disability in the U.S. Even as acute care for strokes advances, there are limited options for improving function once the patient reaches the subacute and chronic stages. Identification of new therapeutic approaches is critical; and DBS holds promise for these patients. A number of case reports and small case series have reported improvement in movement disorders after strokes in patients treated with DBS. In a systematic review, these investigators examined the

patient characteristics, anatomical targets, stimulation parameters, and outcomes of patients who have undergone DBS treatment for post-stroke movement disorders. The PRISMA guidelines were followed. The PubMed, Scopus, and SpringerLink databases were searched for the keywords "DBS", "stroke", "movement" and "recovery" to identify patients treated with DBS for movement disorders after a stroke. The Joanna Briggs Institute Critical Appraisal checklists for case reports and case series were used to systematically analyze the quality of the included studies. Data collected from each study included patient demographic characteristics, stroke diagnosis, movement disorder, DBS target, stimulation parameters, complications, and outcomes. These researchers included 29 studies that described 53 patients who underwent placement of 82 total electrodes. Movement disorders included tremor (n = 18), dystonia (n = 18), hemiballism (n = 6), spastic hemiparesis (n = 1), chorea (n = 1), and mixed disorders (n = 9). The most common DBS targets were the globus pallidus internus (n = 32), VIN of thalamus (n = 25), and subthalamic area/subthalamic nucleus (n = 7). Mono-polar stimulation was reported in 43 leads and bi-polar stimulation in 13. High-frequency stimulation was used in 57 leads and low-frequency stimulation in 6. All patients but 1 had improvement in their movement disorders. Two complications were reported: speech impairment in 1 patient and hardware infection in another. The median (IQR) duration between stroke and DBS treatment was 6.5 (2.1 to 15.8) years. The authors concluded that this was the 1st systematic review of DBS for post-stroke movement disorders. Overall, most studies to-date have been case reports and small series reporting heterogeneous patients and surgical strategies. The findings of this review suggested that DBS for movement disorders after a stroke has the potential to be safe and effective for diverse patients, and DBS may be a feasible option to improve function even years after a stroke.

Orthostatic Tremor

Boogers et al (2022) stated that orthostatic tremor is a rare and debilitating movement disorder; its 1st-line treatment is pharmacological. For pharmacotherapy-refractory patients, surgical therapeutic options such as DBS and SCS have been examined recently. In a systematic review, these investigators examined safety and outcome data on DBS and SCS for patients with orthostatic tremor. They searched PubMed and Embase for studies examining orthostatic tremor patients treated with DBS or SCS. These researchers collected all available safety and outcome data; and the

primary endpoint was the change in unsupported stance duration 1 year post-operatively (± 6 months). The search identified 15 studies, reporting on 32 orthostatic tremor patients who underwent DBS, 4 patients SCS and 2 both. The VIN and the zona incerta were targeted in 25/34 and 9/34 DBS cases, respectively. The median stance time at 1 year follow-up was 240 s compared to 30 s pre-operatively ($p < 0.001$). Stimulation-induced side effects occurred in the majority of patients; however, they were often transient. Bilateral stimulation appeared more effective than unilateral and stimulation settings were comparable to thalamic DBS for ET. There were insufficient data available to draw meaningful conclusions regarding the long-term effects of DBS. Due to insufficient data, no conclusions could be drawn on the effects of SCS on orthostatic tremor. The authors concluded that DBS may be effective to increase stance time in orthostatic tremor patients in the 1st year; however, further investigation is needed to examine the long-term effects and the role of SCS.

Status Dystonicus

Vogt et al (2023) ought to better understand the work-flow, outcomes, and complications of DBS for pediatric status dystonicus (SD). These investigators presented a systematic review, alongside a multi-center case series of pediatric patients with SD treated with DBS. They collected individual data regarding treatment, stimulation parameters, and dystonia severity for a multi-center case series (n = 8) and all previously published cases (n = 77). Data for case series were used to create probabilistic voxel-wise maps of stimulated tissue associated with dystonia improvement. In the institutional series, DBS was implanted a mean of 25 days after SD onset. Programming began a mean of 1.6 days after surgery. All 8 patients in the case series and 73 of 74 reported patients in the systematic review had resolution of their SD with DBS, most within 2 to 4 weeks of surgery. Mean follow-up for patients in the case series was 16 months. DBS target for all patients in the case series and 68 of 77 in the systematic review was the globus pallidus pars interna (GPi). In the case series, stimulation of the posterior-ventrolateral GPi was associated with improved dystonia. Mean dystonia improvement was 32 % and 51 % in the institutional series and systematic review, respectively. Mortality was 4 % in the review, which was lower than that reported for treatment with pharmacotherapy alone (10 % to 12.5 %). The authors concluded that DBS was a feasible intervention with potential to reverse refractory

pediatric SD and improve survival. Moreover, these researchers stated that further investigation is needed to increase awareness of DBS in this setting, so that it can be implemented in a timely manner.

Substance Use Disorder

Shaheen et al (2023) noted that substance use disorder (SUD) is a significant public health issue with a high mortality rate; and DBS has shown promising results in treating SUD in certain cases. In a meta-analysis, these researchers examined the effectiveness of DBS in the treatment of SUD and reduction of relapse rates. They carried out a thorough and methodical search of the existing scientific literature, adhering to the PRISMA guidelines,. These researchers identified 16 original studies that met the inclusion criteria. They used the evidence levels recommended by the Oxford Centre for Evidence-Based Medicine to assess bias. The R version 4.2.3 software was employed to calculate the mean effect size. These researchers estimated study heterogeneity by employing tau2 and I2 indices and conducting Cochran's Q test. The results showed that DBS treatment resulted in a significant improvement in the clinical SUD scales of patients, with an average improvement of 59.6 %. The observed relapse rate was 8 %. The meta-analysis estimated a mean effect size of 55.9 (40.4 to 71.4). Heterogeneity analysis showed a large degree of heterogeneity among the included studies. Subgroup and meta-regression analysis based on age and SUD type suggested that DBS may be more effective for patients above 45 years of age, and for alcohol and opioid addiction compared to nicotine addiction. The authors concluded that available evidence suggests that DBS has a moderate effect on SUD symptoms; and that DBS has the potential to serve as a valuable adjunct to best medical therapy or even as a stand-alone treatment for substance use disorder. Moreover, these researchers stated that the limited number of studies and small sample size indicated that larger, standardized RCTs are needed to examine the effect of DBS on substance use disorder in greater detail, including the factors that contribute to these findings through subgroup analysis.

Tourette Syndrome

Welter et al (2017) noted that DBS has been proposed for the treatment of patients with severe TS; open-label studies and 2 small double-blind trials have tested DBS of the posterior and the anterior internal globus pallidus (aGPi). In a randomized, double-blind,

controlled trial, these investigators examined the effectiveness of aGPi DBS for severe TS. They enrolled patients aged 18 to 60 years with severe and medically refractory TS from 8hospitals specialized in movement disorders in France. Enrolled patients received surgery to implant bilateral electrodes for aGPi DBS; 3 months later they were randomly assigned (1:1 ratio with a block size of 8; computer-generated pair-wise randomization according to order of enrolment) to receive either active or sham stimulation for the subsequent 3 months in a double-blind fashion. All patients then received open-label active stimulation for the subsequent 6 months. Patients and clinicians assessing outcomes were masked to treatment allocation; an unmasked clinician was responsible for stimulation parameter programming, with intensity set below the side-effect threshold. The primary endpoint was difference in Yale Global Tic Severity Scale (YGTSS) score between the beginning and end of the 3 month double-blind period, as assessed with a Mann-Whitney-Wilcoxon test in all randomly allocated patients who received active or sham stimulation during the double-blind period. These researchers examined safety in all patients who were enrolled and received surgery for aGPi DBS. Between December 6, 2007 and December 13, 2012, these investigators enrolled 19 patients. The authors randomly assigned 17 (89 %) patients, with 16 completing blinded assessments (7 [44 %] in the active stimulation group and 9 [56 %] in the sham stimulation group). These researchers noted no significant difference in YGTSS score change between the beginning and the end of the 3 month double-blind period between groups (active group median YGTSS score 68.5 [IQR 34.0 to 83.5] at the beginning and 62.5 [51.5 to 72.0] at the end, median change 1.1 % [IQR -23.9 to 38.1]; sham group 73.0 [69.0 to 79.0] and 79.0 [59.0 to 81.5], median change 0.0 % [-10.6 to 4.8]; p = 0.39). A total of 15 serious adverse events (AEs; 3 in patients who withdrew before stimulation and 6 each in the active and sham stimulation groups) occurred in 13 patients (3 who withdrew before randomization, 4 in the active group, and 6 in the sham group), with infections in DBS hardware in 4 patients (2 who withdrew before randomization, 1 in the sham stimulation group, and 1 in the active stimulation group). Other serious AEs included 1 electrode misplacement (active stimulation group), 1 episode of depressive signs (active stimulation group), and 3 episodes of increased tic severity and anxiety (2 in the sham stimulation group and 1 in the active stimulation group). The authors concluded that 3 months of aGPi DBS was insufficient to decrease tic severity for patients with TS. Moreover,

these researchers stated that larger studies with longer follow-up are needed to establish which factors contribute to the post-operative outcome, especially co-morbidities, notably with respect to QOL and ability to function in social and work environments. These researchers stated that they still lack comparative studies needed to establish the best benefit to risk ratio of DBS for treatment of patients with TS.

Kisten et al (2022) examined the outcome of tics and non-tic related symptomatology in refractory TS treated with antero-medial globus pallidus interna (amGPi) DBS. This trial included all patients with refractory TS (January 2013 to August 2020) from the Brain Nerve Centre and Steve Biko Academic Hospital, Pretoria, South Africa, treated with bilateral amGPi DBS; retrospective baseline, early (up to 3 months) post-DBS follow-up assessment data, as well as prospective data from the latest follow-up (mean of 37.4 months) were collected using standardized scoring tools and scales. A total of 5 patients were identified. Tics decreased by 63.9 % ($p = 0.002$); QOL improved by 39.8 % ($p = 0.015$); self-injurious behavior ceased; obsessive-compulsive symptoms resolved in all but 1. The number of different chronic medications used more than halved. Transient stimulation-related adverse events (AEs) occurred in 4 patients. The authors concluded that this study contributed to the data of the effectiveness of amGPi-targeted DBS in refractory TS, showing improvement in QOL and both tic- and non-tic-related symptomatology. Moreover, these researchers stated that larger numbers of patients are needed to explain the conflicting reported outcomes in motor and non-motor symptoms in patients in blinded and open-label trials of DBS in TS.

The authors stated that this study was limited by the small number of patients and the lack of controls but aided by the long follow-up duration (mean of 37.4 months) showing benefit in real-world practice. Precise connectomic analysis of the anatomical target in the amGPi and stimulation parameters will also require further study to optimize outcome of DBS in Tourette syndrome in the future, and it remains to be determined whether a multi-target stimulation approach may be superior to carefully selected single target lead placing in refractory TS.

Tomskiy et al (2022) stated that TS is a heterogeneous disorder; clinical presentation includes both multiple motor and vocal tics and commonly associated psychiatric conditions (OCD, attention deficit hyperactivity disorder [ADHD], depression, anxiety, etc.). Therapeutic

options primarily consist of non-pharmacological interventions (habit reversal training, relaxation techniques, cognitive behavioral therapy [CBT], and social rehabilitation) and pharmacotherapy. In case of the intractable forms, neurosurgical treatment may be considered, primarily DBS, which appears to be effective in medically intractable TS patients, although, the preferential brain target is still not defined. The majority of studies described small number of cases and the issues of appropriate patient selection and ethics remain to be clarified. The authors reviewed the main points in management of TS, discussed possible indications and contraindications for neurosurgical treatment, and analyzed their experience of DBS in a case series of refractory TS patients with the focus on target selection and individual outcomes.

In a retrospective study, Cui et al (2022) examined the long-term effectiveness, prognostic factors, and safety of postero-ventral globus pallidus internus DBS in patients with refractory TS (RTS). This trial recruited 61 patients with RTS who underwent postero-ventral GPi DBS from January 2010 to December 2020 at the Chinese People's Liberation Army General Hospital. The YGTSS, YBOCS, Beck Depression Inventory (BDI), Gilles de la Tourette Syndrome Quality-of-Life Scale (GTS-QOL) were used to evaluate the pre-operative and post-operative clinical condition in all patients. Prognostic factors and AEs following surgery were analyzed. Patient follow-up was conducted for an average of 73.33 ± 28.44 months. The final post-operative YGTSS (32.39 ± 22.34 versus 76.61 ± 17.07), YBOCS (11.26 ± 5.57 versus 18.31 ± 8.55), BDI (14.36 ± 8.16 versus 24.79 ± 11.03) and GTS-QOL (39.69 ± 18.29 versus 78.08 ± 14.52) scores at the end of the follow-up period were significantly lower than those before the surgery ($p < 0.05$). While age and the duration of follow-up were closely related to prognosis, the disease duration and gender were not. No serious AEs were observed and only 1 patient exhibited symptomatic deterioration. The authors concluded that postero-ventral-GPi DBS provided long-term effectiveness, acceptable safety and could improve the QOL in RTS patients. Moreover, DBS is more successful among younger patients and with longer treatment duration.

Lin et al (2022) carried out a systematic literature search for RCTs. A network meta-analysis by R4.04 software according to Bayesian framework were performed. Results were meta-analyzed and network meta-analyzed to compare the effectiveness of DBS, rTMS, and behavioral therapy (BT) in TS patients. A total of 18 RCTs with 661

participants were included. The YGTSS and the Y-BOCS were utilized to evaluate the symptoms of TS. All 3 treatments improved the tic symptoms of TS [DBS 12.11 (95 % CI: 7.58 to 16.65); rTMS 4.96 (95 % CI: 1.01 to 10.93); and BT 11.72 (95 %CI: 10.42 to 13.01)]; and obsessive-compulsive symptom [DBS 4.9 (95 %CI: 1.13 to 8.67); rTMS 5.28 (95 % CI: 0.21 to 10.77); and BT 1.61 (95 % CI: 0.74 to 2.48)]. The cumulative probability results showed that DBS had the best effect on the improvement of tic symptoms, followed by BT; and rTMS was ranked last. However, in terms of improvement of obsessional symptoms, rTMS was ranked first, DBS was ranked second, and BT was ranked last. Furthermore, the meta regression analysis of YGTSS in DBS, rTMS and BT had significant difference (p = 0.05). The authors concluded that this study showed that DBS, rTMS, and BT were effective in TS. DBS causes the best improvement in tic symptoms, and rTMS was the most effective in improving the obsessive-compulsive symptoms.

The authors stated that this review/analysis had several drawbacks. First, the target and parament of DBS and rTMS were not under consideration. Second, the adverse effect of therapies was quite different. These researchers described the adverse effect of therapy methods; however, they did not analyze the adverse reactions because of the lack of a quantitative index. Third, these findings, while borne out by rigorous statistical analyses, may not capture the full complexity of variable individual responses to one treatment or another -- or one target or another -- and that further head-to-head studies are needed to further elucidate optimal therapeutic approaches.

In a retrospective, cohort study, Wang et al (2024) examined the safety and effectiveness of combined DBS with anterior capsulotomy for co-morbid motor and psychiatric symptoms in patients with TS. This trial enrolled TS patients with co-morbid motor and psychiatric symptoms who were treated with combined DBS and anterior capsulotomy at the authors' center. Longitudinal motor, psychiatric, and cognitive outcomes, and QOL were assessed. In addition, a systematic review and meta-analysis were performed to summarize the current experience with the available evidence. A total of 5 eligible patients in this cohort and 26 summarized patients in 6 cohorts were included. After a mean 18-month follow-up, the authors' cohort reported that motor symptoms significantly improved by 62.4 % (p = 0.005); psychiatric symptoms of OCD and anxiety significantly improved by

87.7 % ($p < 0.001$) and 78.4 % ($p = 0.009$); QOL significantly improved by 61.9 % ($p = 0.011$); and no significant difference was found in cognitive function (all $p > 0.05$). Combined surgery resulted in greater improvements in psychiatric outcomes and QOL than DBS alone. The synthesized findings suggested significant improvements in tics (MD: 57.92, 95 % CI: 41.28 to 74.56, $p < 0.001$), OCD (MD: 21.91, 95 % CI: 18.67 to 25.15, $p < 0.001$), depression (MD: 18.32, 95 % CI: 13.26 to 23.38, $p < 0.001$), anxiety (MD: 13.83, 95 % CI: 11.90 to 15.76, $p < 0.001$), and QOL (MD: 48.22, 95 % CI: 43.68 to 52.77, $p < 0.001$). Individual analysis showed that the pooled treatment effects on motor symptoms, psychiatric symptoms, and QOL were 78.6 %, 84.5 % to 87.9 %, and 83.0 %, respectively. The overall pooled rate of AEs was 50.0 %, and all of these AEs were resolved or alleviated with favorable outcomes. The authors concluded that combined DBS with capsulotomy was effective for relieving motor and psychiatric symptoms in TS patients, and its safety was acceptable. Moreover, these researchers stated that the optimal candidate should be considered, and additional experience is still needed. This was a relatively small study; and its findings were confounded by the combined approach of DBS and capsulotomy. If these findings are replicated in prospective, controlled studies, these combination approaches might become a therapeutic option.

In a review on Tourettic OCD (TOCD), Katz et al (2022) stated that DBS therapy is invasive, may have side effects and has not been approved for use in the pediatric population. Furthermore, the optimal targets for symptom control may need to be individualized. These researchers stated that future efforts of combining fMRI with stereotactic surgery may aid in determining the best targets for patients with TOCD.

Furthermore, an UpToDate review on “Tourette syndrome: Management” (Jankovic, 2024) states that “Patients with TS who have disabling tics that are refractory to optimal medical management, including various dopamine depleters and dopamine receptor blockers, may be candidates for deep brain stimulation (DBS) of globus pallidus, thalamus, or other subcortical targets. Preliminary evidence, while inconsistent, suggests that DBS can lead to symptomatic improvement in tics but is associated with a high rate of adverse events. Larger clinical trials are needed to determine whether DBS is safe and beneficial for controlling tics in patients with TS”.

Anoxic Brain Injury

Gao et al (2020) stated that post-hypoxic myoclonus (PHM) is characterized by generalized myoclonus following hypoxic brain injury. Myoclonus is often functionally impairing and refractory to medical therapies; DBS has been employed for the treatment of myoclonus-dystonia; however, few cases of PHM have been described. These researchers reported on the case of a 33-year-old woman who developed severe, refractory generalized myoclonus following cardio-pulmonary arrest from drowning. They carried out MRI-guided asleep bilateral pallidal DBS placement, resulting in improvement in action myoclonus at 1 year. The authors concluded that the findings of this case contributed to growing evidence regarding the use of DBS for the treatment of PHM. These investigators stated that interventional MRI-guided DBS technique could be used for safe and accurate lead placement. This was the first case to describe asleep, interventional MRI-guided technique for implanting DBS leads in the treatment of patients with PHM. Moreover, these researchers stated that additional clinical trials with more structured protocol for patient selection, systematic programming guidelines, as well as blinded, and objective assessment of improvement are needed.

Mure et al (2020) noted that the Lance-Adams syndrome (LAS) is a myoclonus syndrome caused by hypoxic-ischemic encephalopathy. LAS cases could be refractory to 1st-line medications, and the neuronal mechanism underlying LAS pathology remains unknown. These researchers described a patient with LAS who underwent bilateral GPi stimulation and discussed the pathophysiology of LAS with intra-operative electrophysiological findings. This case entailed a 79-year-old woman who presented with a history of cardio-pulmonary arrest due to internal carotid artery rupture after carotid endarterectomy following successful cardio-pulmonary resuscitation. However, within 1 month, the subject developed sensory stimulation-induced myoclonus in her face as well as extremities. Because her myoclonic symptoms were refractory to pharmacotherapy, DBS of the GPi was carried out 1 year after the hypoxic attack. Continuous bilateral GPi stimulation with optimal parameter settings remarkably improved the patient's myoclonic symptoms. At the 2-year follow-up, her Unified Myoclonus Rating Scale (UMRS) score decreased from 90 to 24. Furthermore, these investigators observed burst firing and inter-burst pause patterns on intra-operative microelectrode recordings of the bilateral GPi and stimulated this area as the therapeutic target. The authors concluded

that the findings of this study demonstrated that impairment in the basal ganglion circuitry might be involved in the pathogenesis of myoclonus in patients with LAS.

Ahmed (2023) noted that PHM is a rare neurological complication having 2 different variants depending on acute or chronic onset following cardio-pulmonary resuscitation after cardiac arrest -- myoclonic status epilepticus (MSE) and LAS, respectively. Clinical as well as simultaneous EEG and electromyographic (EMG) tracing could distinguish between the two. Anecdotal treatment with benzodiazepines and anesthetics (in the case of MSE) have been employed. Although limited evidence is available, valproic acid, clonazepam and levetiracetam, either in combination with other drugs or alone, have shown to effectively control epilepsy associated with LAS. Moreover, the author stated that DBS is a novel and promising advance in the treatment of patients with LAS.

References

The above policy is based on the following references:

1. Abdi S. Prevention and management of complex regional pain syndrome in adults. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed October 2012.
2. Abelson JL, Curtis GC, Sagher O, et al. Deep brain stimulation for refractory obsessive-compulsive disorder. Biol Psychiatry. 2005;57(5):510-516.
3. Abramowitz JS, Taylor S, McKay D. Obsessive-compulsive disorder. Lancet. 2009;374(9688):491-499.
4. Ahmed HS. Post-hypoxic myoclonus; what we know and gaps in knowledge. Trop Doct. 2023;53(4):460-463.
5. Akram H, Miller S, Lagrata S, et al. Ventral tegmental area deep brain stimulation for refractory chronic cluster headache. Neurology. 2016;86(18):1676-1682.
6. Alanazi RF, Alkhani AM. Management of Lennox-Gastaut syndrome with deep brain stimulation: A systematic literature review. Neurosciences (Riyadh). 2022;27(4):216-220.

7. Alesch F, et al. Stimulation of the ventral intermediate thalamic nucleus in tremor dominated Parkinson's disease and essential tremor. Acta Neurochir. 1995;136:75-81.
8. Alonso P, Cuadras D, Gabriels L, et al. Deep brain stimulation for obsessive-compulsive disorder: A meta-analysis of treatment outcome and predictors of response. PLoS One. 2015;10(7):e0133591.
9. Alterman RL, Reiter GT, Shils J, et al. Targeting for thalamic deep brain stimulator implantation without computer guidance: assessment of targeting accuracy. Stereotact Funct Neurosurg. 1999;72(2-4): 150-153.
10. Anderson VC, Burchiel KJ, Hogarth P, et al. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. Arch Neurol. 2005;62(4):554-560.
11. Anouti A, Koller WC. Tremor disorders: Diagnosis and management. West J Med. 1995;162:510-513.
12. Bartsch C, Kuhn J.[Deep brain stimulation for addiction, anorexia and compulsion. Rationale, clinical results and ethical implications. Nervenarzt. 2014;85(2):162-168.
13. Benabid AL, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg. 1996;84:203-214.
14. Bergfeld IO, Mantione M, Hoogendoorn ML, et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: A randomized clinical trial. JAMA Psychiatry. 2016;73(5):456-464.
15. Berlim MT, McGirr A, Van den Eynde F, et al. Effectiveness and acceptability of deep brain stimulation (DBS) of the subgenual cingulate cortex for treatment-resistant depression: A systematic review and exploratory meta-analysis. J Affect Disord. 2014;159:31-38.
16. Blond S, et al. Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. J Neurosurg. 1992;77:62-68.
17. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Bilateral DBS of the subthalamic nucleus or the globus pallidus interna for treatment of advanced Parkinson's disease. TEC Assessment Program. Chicago, IL: BCBSA; February 2002;16(16).
18. Bonomo R, Elia AE, Bonomo G, et al. Deep brain stimulation in Huntington's disease: A literature review. Neurol Sci.

2021;42(11):4447-4457.

19. Boogers A, Billet A, Vandenberghe W, et al. Deep brain stimulation and spinal cord stimulation for orthostatic tremor: A systematic review. Parkinsonism Relat Disord. 2022;104:115-120.
20. Bouwens van der Vlis TAM, Schijns OEMG, Schaper FLWVJ, et al. Deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy. Neurosurg Rev. 2019;42(2):287-296.
21. Brandmeir NJ, Murray A, Cheyuo C, et al. Deep brain stimulation for multiple sclerosis tremor: A meta-analysis. Neuromodulation. 2020;23(4):463-468.
22. Bronte-Stewart H. New Drugs and Devices. Deep brain stimulation. Neurol Clin Prac. 2012;291):67-71.
23. Burchiel KJ, Anderson VC, Favre J, et al. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: Results of a randomized, blinded pilot study. Neurosurgery. 1999;45(6):1375-1384.
24. Canadian Coordinating Office for Health Technology Assessment (CCOHTA). Deep brain stimulation for patients with Parkinson's disease. Pre-Assessment No. 14. Ottawa, ON: CCOHTA; December 2002.
25. Carpenter LL, Friehs GM, Tyrka AR, et al. Vagus nerve stimulation and deep brain stimulation for treatment resistant depression. Med Health R I. 2006;89(4):137, 140-141.
26. Carpinella I, Crenna P, Marzegan A, et al. Effect of L-dopa and subthalamic nucleus stimulation on arm and leg swing during gait in Parkinson's Disease. Annu Int Conf IEEE Eng Med Biol Soc. 2007;2007:6665-6668.
27. Chang B, Xu J. Deep brain stimulation for refractory temporal lobe epilepsy: A systematic review and meta-analysis with an emphasis on alleviation of seizure frequency outcome. Childs Nerv Syst. 2018;34(2):321-327.
28. Chang R, Peng J, Chen Y, et al. Deep brain stimulation in drug addiction treatment: Research progress and perspective. Front Psychiatry. 2022;13:858638.
29. Cheyuo C, Germann J, Yamamoto K, et al. Connectomic neuromodulation for Alzheimer's disease: A systematic review and meta-analysis of invasive and non-invasive techniques. Transl Psychiatry. 2022;12(1):490.

30. Chieng LO, Madhavan K, Wang MY. Deep brain stimulation as a treatment for Parkinson's disease related camptocormia. J Clin Neurosci. 2015;22(10):1555-1561.
31. Clarke C, Moore AP. Parkinson's disease. In: Clinical Evidence. London, UK: BMJ Publishing Group; updated May 2004.
32. Collins TR. Brain stimulation device found to reduce seizures in randomized trial. Neurology Today, October 21, 2010. pg. 14.
33. Cossu G, Pau M. (Subthalamic nucleus stimulation and gait in Parkinson's Disease: A not always fruitful relationship. Gait Posture. 2017;52:205-210.
34. Crowell AL, Riva-Posse P, Holtzheimer PE, et al. Long-term outcomes of subcallosal cingulate deep brain stimulation for treatment-resistant depression. Am J Psychiatry. 2019;176(11):949-956.
35. Cruccu G, Aziz TZ, Garcia-Larrea L, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol. 2007;14(9):952-970.
36. Cui Z-Q, Wang J, Mao Z-Q, et al. Long-term efficacy, prognostic factors, and safety of deep brain stimulation in patients with refractory Tourette syndrome: A single center, single target, retrospective study. J Psychiatr Res. 2022;151:523-530.
37. Dalic LJ, Warren AEL, Bulluss KJ, et al. DBS of thalamic centromedian nucleus for Lennox-Gastaut syndrome (ESTEL Trial). Ann Neurol. 2022a;91(2):253-267.
38. Dalic LJ, Warren AEL, Malpas CB, et al. Cognition, adaptive skills and epilepsy disability/severity in patients with Lennox-Gastaut syndrome undergoing deep brain stimulation for epilepsy in the ESTEL trial. Seizure. 2022b;101:67-74.
39. Defebvre LJ, Blatt JL, Blond SC, et al. Effect of long-term stimulation of the ventral intermediate thalamic nucleus on gait in Parkinson's disease. Adv Neurol. 1999;80:627-630.
40. Denys D, de Koning PP. Deep brain stimulation for treatment of obsessive-compulsive disorder. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed November 2013.
41. Deuschl G, Bain P. Deep brain stimulation for tremor [correction of trauma]: Patient selection and evaluation. Mov Disord. 2002;17 Suppl 3:S102-S111.
42. Deuschl G. Neurostimulation for Parkinson disease. JAMA. 2009;301(1):104-105.
43. Di GiulioI, Kalliolia E, Georgiev D, et al. Chronic subthalamic nucleus stimulation in Parkinson's disease: Optimal frequency

for gait depends on stimulation site and axial symptoms. Front Neurol. 2019;10:29.

44. Drislane FW. Convulsive status epilepticus in adults: Management. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2022.
45. Eitan R, Lerer B. Nonpharmacological, somatic treatments of depression: Electroconvulsive therapy and novel brain stimulation modalities. Dialogues Clin Neurosci. 2006;8(2):241-258.
46. Ekbom K, Waldenlind E. Cluster headache: The history of the Cluster Club and a review of recent clinical research. Funct Neurol. 2004;19(2):73-81.
47. Eltahawy HA, Saint-Cyr J, Poon YY, et al. Pallidal deep brain stimulation in cervical dystonia: Clinical outcome in four cases. Can J Neurol Sci. 2004;31(3):328-332.
48. Eskandar EN, Cosgrove GR, Shinobu LA. Surgical treatment of Parkinson Disease. JAMA. 2001;286(24):3056-3059.
49. Eskandari K, Fattahi M, Yazdanian H, Haghparast A. Is deep brain stimulation an effective treatment for psychostimulant dependency? A preclinical and clinical systematic review. Neurochem Res. 2023;48(5):1255-1268
50. Faist M, Xie J, Kurz D, et al. Effect of bilateral subthalamic nucleus stimulation on gait in Parkinson's disease. Brain. 2001;124(Pt 8):1590-1600.
51. Farrell A, Theodoros D, Ward E, et al. Effects of neurosurgical management of Parkinson's disease on speech characteristics and oromotor function. J Speech Lang Hear Res. 2005;48(1):5-20.
52. Fattahi M, Eskandari K, Sayehmiri F, et al. Deep brain stimulation for opioid use disorder: A systematic review of preclinical and clinical evidence. Brain Res Bull. 2022;187:39-48.
53. Ferrarin M, Lopiano L, Rizzone M, et al. Quantitative analysis of gait in Parkinson's disease: A pilot study on the effects of bilateral sub-thalamic stimulation. Gait Posture; 2002;16(2):135-148.
54. Ferrarin M, Rizzone M, Bergamasco B, et al. Effects of bilateral subthalamic stimulation on gait kinematics and kinetics in Parkinson's disease. Exp Brain Res. 2005;160(4):517-527.
55. Ferrarin M, Rizzone M, Lopiano L, et al. Effects of subthalamic nucleus stimulation and L-dopa in trunk kinematics of patients

with Parkinson's disease. Gait Posture. 2004;19(2):164-171.
56. Fields JA, Troster AI, Woods SP, et al. Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor. J Neurol Neurosurg Psychiatry. 2003;74(3):305-311.
57. Figueiras-Mendez R, et al. Further supporting evidence of beneficial subthalamic stimulation in Parkinson's patients. Neurology. 2002;58:469-470.
58. Fins JJ, Mayberg HS, Nuttin B, et al. Misuse of the FDA's humanitarian device exemption in deep brain stimulation for obsessive-compulsive disorder. Health Aff (Millwood). 2011;30(2):302-311.
59. Fisher R, Salanova V, Witt T, et al; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;51(5):899-908.
60. Foote KD, Seignourel P, Fernandez HH, et al. Dual electrode thalamic deep brain stimulation for the treatment of posttraumatic and multiple sclerosis tremor. Neurosurgery. 2006;58(4 Suppl 2):ONS-280-285; discussion ONS-285-286.
61. Fountas KN, Kapsalaki E, Hadjigeorgiou G. Cerebellar stimulation in the management of medically intractable epilepsy: A systematic and critical review. Neurosurg Focus. 2010;29(2):E8.
62. Fraix V, Pollak P, Van Blercom N, et al. Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia in Parkinson's disease. Neurology. 2000; 55:1921-1923.
63. Fransson PA, Nilsson MH, Niehorster DC, et al. Exploring the effects of deep brain stimulation and vision on tremor in Parkinson's disease -- benefits from objective methods. J Neuroeng Rehabil. 2020;17(1):56.
64. Frizon LA, Yamamoto EA, Nagel SJ, et al. Deep brain stimulation for pain in the modern era: A systematic review. Neurosurgery. 2020;86(2):191-202.
65. Galvez-Jimenez N, Lozano A, Tasker R, et al. Pallidal stimulation in Parkinson's disease patients with a prior unilateral pallidotomy. Can J Neurol Sci. 1998;25(4):300-305.
66. Gao F, Ostrem JL, Wang DD. Treatment of post-hypoxic myoclonus using pallidal deep brain stimulation placed using interventional MRI methods. Tremor Other Hyperkinet Mov (N Y). 2020;10:42.

67. Georgiopoulos M, Katsakiori P, Kefalopoulou Z, et al. Vegetative state and minimally conscious state: A review of the therapeutic interventions. Stereotact Funct Neurosurg. 2010;88(4):199-207.
68. Gerschlager W, Alesch F, Cunnington R, et al. Bilateral subthalamic nucleus stimulation improves frontal cortex function in Parkinson's disease. An electrophysiological study of the contingent negative variation. Brain. 1999;122 (Pt 12):2365-2373.
69. Gervais-Bernard H, Xie-Brustolin J, Mertens P, et al. Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: Five year follow-up. J Neurol. 2009;256(2):225-233.
70. Giacino J, Fins JJ, Machado A, Schiff ND. Central thalamic deep brain stimulation to promote recovery from chronic posttraumatic minimally conscious state: Challenges and opportunities. Neuromodulation. 2012;15(4):339-349.
71. Giller C, Mehta S, Yanasak N, Jenkins P. Avoidance of electrode related MRI artifact during staged deep brain stimulator implantation. J Neurol Surg A Cent Eur Neurosurg. 2012;73(5):320-323.
72. Giordano F, Cavallo M, Spacca B, et al. Deep brain stimulation of the anterior limb of the internal capsule may be efficacious for explosive aggressive behaviour. Stereotact Funct Neurosurg. 2016;94(6):371-378.
73. Golestanirad L, Elahi B, Graham SJ, et al. Efficacy and safety of pedunculopontine nuclei (PPN) deep brain stimulation in the treatment of gait disorders: A meta-analysis of clinical studies. Can J Neurol Sci. 2016;43(1):120-126.
74. Goodman JH. Brain stimulation as a therapy for epilepsy. Adv Exp Med Biol. 2004;548:239-247.
75. Grasso R, Peppe A, Stratta F, et al. Basal ganglia and gait control: apomorphine administration and internal pallidum stimulation in Parkinson's disease. Exp Brain Res. 1999;126(2):139-148.
76. Greenberg BD, Rezai AR. Mechanisms and the current state of deep brain stimulation in neuropsychiatry. CNS Spectr. 2003;8(7):522-526.
77. Hacker ML, DeLong MR, Turchan M, et al. Effects of deep brain stimulation on rest tremor progression in early stage Parkinson disease. Neurology. 2018;91(5):e463-e471.

78. Hallett M, Evinger C, Jankovic J, Stacy M; BEBRF International Workshop. Update on blepharospasm: Report from the BEBRF International Workshop. Neurology. 2008;71(16):1275-1282.
79. Halpern CH, Torres N, Hurtig HI, et al. Expanding applications of deep brain stimulation: A potential therapeutic role in obesity and addiction management. Acta Neurochir (Wien). 2011;153(12):2293-2306.
80. Halpern CH, Wolf JA, Bale TL, et al. Deep brain stimulation in the treatment of obesity. J Neurosurg. 2008;109(4):625-634.
81. Hamel W, Herzog J, Kopper F, et al. Deep brain stimulation in the subthalamic area is more effective than nucleus ventralis intermedius stimulation for bilateral intention tremor. Acta Neurochir (Wien). 2007;149(8):749-758; discussion 758.
82. Hardenacke K, Shubina E, Bührle CP, et al. Deep brain stimulation as a tool for improving cognitive functioning in Alzheimer's dementia: A systematic review. Front Psychiatry. 2013;4:159.
83. Hassan A, Ahlskog JE, Matsumoto JY, et al. Orthostatic tremor: Clinical, electrophysiologic, and treatment findings in 184 patients. Neurology. 2016;86(5):458-464.
84. Hescham S, Lim LW, Jahanshahi A, et al. Deep brain stimulation in dementia-related disorders. Neurosci Biobehav Rev. 2013;37(10 Pt 2):2666-2675.
85. Hewitt AL, Klassen BT, Lee KH, et al. Deep brain stimulation for orthostatic tremor: A single-center case series. Neurol Clin Pract. 2020;10(4):324-332.
86. Holtzheimer PE, Kelley ME, Gross RE, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry. 2012;69(2):150-158.
87. Holtzheimer PE 3rd, Nemeroff CB. Advances in the treatment of depression. NeuroRx. 2006;3(1):42-56.
88. Houeto JL, Karachi C, Mallet L, et al. Tourette's syndrome and deep brain stimulation. J Neurol Neurosurg Psychiatry. 2005;76(7):992-995.
89. Hsu TI, Nguyen A, Gupta N, et al. Effectiveness of deep brain stimulation in treatment of anorexia nervosa and obesity: A systematic review. World Neurosurg. 2022;168:179-189.
90. Hubble JP, et al. Deep brain stimulation for essential tremor. Neurology. 1996;46:1150-1153.

91. Husted DS, Shapira NA. A review of the treatment for refractory obsessive-compulsive disorder: From medicine to deep brain stimulation. CNS Spectr. 2004;9(11):833-847.
92. Institute for Clinical Systems Improvement (ICSI). Deep brain stimulation for essential tremor and Parkinson's disease. Technology Assessment Report. Bloomington, MN: ICSI; 2000.
93. Jankovic J. Tourette syndrome: Management. UpToDate Inc., Waltham, MA. Last reviewed February 2024.
94. Kang GA, Heath S, Rothlind J, Starr PA. Long-term follow-up of pallidal deep brain stimulation in two cases of Huntington's disease. J Neurol Neurosurg Psychiatry. 2011;82(3):272-277.
95. Katz TC, Bui TH, Worhach J, et al. Tourettic OCD: Current understanding and treatment challenges of a unique endophenotype. Front Psychiatry. 2022;13:929526.
96. Kennedy SH, Giacobbe P, Rizvi SJ, ... Mayberg HS, Lozano AM. Deep brain stimulation for treatment-resistant depression: Follow-up after 3 to 6 years. Am J Psychiatry. 2011;168(5):502-10.
97. Karaszewska D, Cleintuar P, Oudijn M, et al. Efficacy and safety of deep brain stimulation for treatment-refractory anorexia nervosa: A systematic review and meta-analysis. Transl Psychiatry. 2022;12(1):333.
98. Kennedy SH, Milev R, Giacobbe P, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J Affect Disord. 2009;117 Suppl 1:S44-S53.
99. Kim SH, Lim SC, Kim J, et al. Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience. Seizure. 2017;52:154-161.
100. Kisely S, Hall K, Siskind D, et al. Deep brain stimulation for obsessive-compulsive disorder: A systematic review and meta-analysis. Psychol Med. 2014;44(16):3533-3542.
101. Kisten R, van Coller R, Cassimjee N, et al. Efficacy of deep brain stimulation of the anterior-medial globus pallidus internus in tic and non-tic related symptomatology in refractory Tourette syndrome. Clin Park Relat Disord. 2022;7:100159.
102. Klepitskaya O, Liu Y, Sharma S, et al. Deep brain stimulation improves restless legs syndrome in patients with Parkinson disease. Neurology. 2018;91(11):e1013-e1021.

103. Klinger N, Mittal S. Deep brain stimulation for seizure control in drug-resistant epilepsy. Neurosurg Focus. 2018;45(2):E4.
104. Knebel J, McClure RK, Kennedy MLH. Assessing the pharmacotherapy and clinical outcomes after deep brain stimulation for treatment-refractory obsessive-compulsive disorder: A case-cohort study. J Clin Med. 2024;13(21):6549.
105. Koeppen JA, Nahravani F, Kramer M, et al. Electrical stimulation of the anterior thalamus for epilepsy: Clinical outcome and analysis of efficient target. Neuromodulation. 2019;22(4):465-471.
106. Kohl S, Schönherr DM, Luigjes J, et al. Deep brain stimulation for treatment-refractory obsessive compulsive disorder: A systematic review. BMC Psychiatry. 2014;14:214.
107. Kovacs N, Nagy F, Kover F, et al. Implanted deep brain stimulator and 1.0-Tesla magnetic resonance imaging. J Magn Reson Imaging. 2006;24(6):1409-1412.
108. Koy A, Hellmich M, Pauls KA, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: A meta-analysis. Mov Disord. 2013;28(5):647-654.
109. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003;349(20):1925-1934.
110. Krystkowiak P, Blatt JL, Bourriez JL, et al. Effects of subthalamic nucleus stimulation and levodopa treatment on gait abnormalities in Parkinson disease. Arch Neurol. 2003;60(1):80-84.
111. Kuhner A, Wiesmeier IK, Cenciarini M, et al. (2019) Motion biomarkers showing maximum contrast between healthy subjects and Parkinson's disease patients treated with deep brain stimulation of the subthalamic nucleus. A pilot study. Front Neurosci. 2019;13:1450.
112. Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology. 1998;51(3):850-855.
113. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: New clinical, neurobiological, and treatment perspectives. Lancet. 2012;379(9820):1045-1055.
114. L'Agence Nationale d'Accreditation d'Evaluation en Sante (ANAES). Evaluation of deep brain stimulation in idiopathic Parkinson disease. Paris, France: ANAES; 2003.

115. Lemaire JJ, Sontheimer A, Nezzar H, et al. Electrical modulation of neuronal networks in brain-injured patients with disorders of consciousness: A systematic review. Ann Fr Anesth Reanim. 2014;33(2):88-97.
116. Leone M. Chronic cluster headache: New and emerging treatment options. Curr Pain Headache Rep. 2004;8(5):347-352.
117. Levine CB, Fahrbach KR, Siderowf AD, et al. Diagnosis and treatment of Parkinson's Disease: A systematic review of the literature. Evidence Report/Technology Assessment No. 57. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2003.
118. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 1998;339(16):1105-1111.
119. Limousin P, Pollak P, Benazzouz A, et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet. 1995;345(8942):91-95.
120. Limousin-Dowsey P, Pollak P, Van Blercom N, et al. Thalamic, subthalamic nucleus and internal pallidum stimulation in Parkinson's disease. J Neurol. 1999;246 (Suppl 2):II42-II45.
121. Lin X, Lin F, Chen H, et al. Comparison of efficacy of deep brain stimulation, repeat transcranial magnetic stimulation, and behavioral therapy in Tourette syndrome: A systematic review and Bayesian network meta-analysis. Heliyon. 2022;8(10):e10952.
122. Lipsman N, Woodside DB, Giacobbe P, et al. Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: A phase 1 pilot trial. Lancet. 2013;381(9875):1361-1370.
123. Lizarraga KJ, Fasano A. Effects of deep brain stimulation on postural trunk deformities: A systematic review. Mov Disord Clin Pract. 2019;6(8):627-638.
124. Lizarraga KJ, Jagid JR, Luca CC. (2016) Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation on gait kinematics in Parkinson's disease: A randomized, blinded study. J Neurol. 2016;263(8):1652-1656.
125. Lopez WOC, Navarro PA, Crispin S. Effectiveness of deep brain stimulation in reducing body mass index and weight: A systematic review. Stereotact Funct Neurosurg. 2022;100(2):75-85.

126. Lozano AM, Dostrovsky J, Chen R, Ashby P. Deep brain stimulation for Parkinson's disease: Disrupting the disruption. Lancet Neurol. 2002;1(4):225-231.
127. Lozano AM, Mayberg HS, Giacobbe P, et al. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2008;64(6):461-467.
128. Luigjes J, van den Brink W, Feenstra M, et al. Deep brain stimulation in addiction: A review of potential brain targets. Mol Psychiatry. 2012;17(6):572-583.
129. Lyons KE, Pahwa R. Deep brain stimulation and tremor. Neurotherapeutics. 2008;5(2):331-338.
130. Lyons MK, Birch BD, Hillman RA, et al. Long-term follow-up of deep brain stimulation for Meige syndrome. Neurosurg Focus. 2010;29(2):E5.
131. Mallet L, Polosan M, Jaafari N, et al; STOC Study Group. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008;359(20):2121-2134.
132. Mar-Barrutia L, Real E, Segalas C, et al. Deep brain stimulation for obsessive-compulsive disorder: A systematic review of worldwide experience after 20 years. World J Psychiatry. 2021;11(9):659-680.
133. Marks WA, Honeycutt J, Acosta F Jr, et al. Dystonia due to cerebral palsy responds to deep brain stimulation of the globus pallidus internus. Mov Disord. 2011;26(9):1748-1751.
134. Martin AJ, Larson PS, Ziman N et al. Deep brain stimulator implantation in a diagnostic MRI suite: Infection history over a 10-year period. J Neurosurg. 2017a;126(1):108-113.
135. Martin AJ, Starr PA, Ostrem JL, Larson PS. Hemorrhage detection and incidence during magnetic resonance-guided deep brain stimulator implantations. Stereotact Funct Neurosurg. 2017b;95(5):307-314.
136. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45(5):651-660.
137. McKhann GM 2nd. Novel surgical treatments for epilepsy. Curr Neurol Neurosci Rep. 2004;4(4):335-339.
138. Medical Services Advisory Committee (MSAC). Deep brain stimulation for the symptoms of Parkinson's disease. Assessment Report. MSAC Application 1031. Canberra, ACT: MSAC; 2001.

139. Medical Technology Unit-Federal Social Insurance Office Switzerland (MTU-FSIOS). Deep brain stimulation for movement disorders (except Parkinson). Bern, Switzerland: MTU-FSIOS; 2001.
140. Morrell M. Brain stimulation for epilepsy: Can scheduled or responsive neurostimulation stop seizures? Curr Opin Neurol. 2006;19(2):164-168.
141. Mosley PE, Windels F, Morris J, et al. A randomised, double-blind, sham-controlled trial of deep brain stimulation of the bed nucleus of the stria terminalis for treatment-resistant obsessive-compulsive disorder. Transl Psychiatry. 2021;11(1):190.
142. Muller-Vahl KR, Cath DC, Cavanna AE, et al; ESSTS Guidelines Group. European clinical guidelines for Tourette syndrome and other tic disorders. Part IV: Deep brain stimulation. Eur Child Adolesc Psychiatry. 2011;20(4):209-217.
143. Mure H, Toyoda N, Morigaki R, et al. Clinical outcome and intraoperative neurophysiology of the Lance-Adams syndrome treated with bilateral deep brain stimulation of the globus pallidus internus: A case report and review of the literature. Stereotact Funct Neurosurg. 2020;98(6):399-403.
144. Naesstrom M, Blomstedt P, Bodlund O. A systematic review of psychiatric indications for deep brain stimulation, with focus on major depressive and obsessive-compulsive disorder. Nord J Psychiatry. 2016;70(7):483-491.
145. Narang P, Retzlaff A, Brar K, Lippmann S. Deep brain stimulation for treatment-refractory depression. South Med J. 2016;109(11):700-703.
146. National Institute for Clinical Excellence (NICE). Deep brain stimulation for Parkinson's disease. Interventional Procedure Guidance 19. London, UK: NICE; November 2003.
147. National Institute for Health and Clinical Excellence (NICE). Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). Interventional Procedures Overview. London, UK: NICE; April 2006.
148. Nicholson T, Milne R. Pallidotomy, thalamotomy and deep brain stimulation for severe Parkinson's disease. Development and Evaluation Committee (DEC) Report No. 105. Southampton, UK: Wessex Institute for Health Research and Development (WIHRD), University of Southampton; 1999.

149. Nowacki A, Schober M, Nader L, et al. Deep brain stimulation for chronic cluster headache: Meta-analysis of individual patient data. Ann Neurol. 202;88(5):956-969.
150. O'Brien M A, Wingerchuk D, Angle P, et al. Management of chronic central neuropathic pain following traumatic spinal cord injury. Evidence Report/Technology Assessment No. 45. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2001.
151. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): Treatment guidelines. Neurology. 2001;56(Suppl 5):S1-S88.
152. Ontario Ministry of Health and Long-Term Care, Medical Advisory Secretariat. Deep brain stimulation for Parkinson's disease and other movement disorders. Health Technology Assessment. Toronto, ON: Ontario Ministry of Health and Long-Term Care; 2005.
153. Pahwa R, Factor SA, Lyons KE, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66(7):983-995.
154. Pahwa R, Wilkinson S, Smith D, et al. High-frequency stimulation of the globus pallidus for the treatment of Parkinson's disease. Neurology. 1997;49(1):249-253.
155. Pallanti S, Hollander E, Goodman WK. A qualitative analysis of nonresponse: Management of treatment-refractory obsessive-compulsive disorder. J Clin Psychiatry. 2004;65 Suppl 14:6-10.
156. Pan I, Dendukuri N, McGregor M. Subthalamic deep brain stimulation (DBS): Clinical efficacy, safety and cost compared to medical therapy for the treatment of Parkinson's disease. Report No. 38. Montreal, QC: Technology Assessment Unit of the McGill University Health Centre (MUHC); November 27, 2009.
157. Panov F, Gologorsky Y, Connors G, et al. Deep brain stimulation in DYT1 dystonia: A 10-year experience. Neurosurgery. 2013;73(1):86-93; discussion 93.
158. Park HR, Kim IH, Kang H, et al. Nucleus accumbens deep brain stimulation for a patient with self-injurious behavior and autism spectrum disorder: Functional and structural changes

of the brain: Report of a case and review of literature. Acta Neurochir (Wien). 2017;159(1):137-143.

159. Paro MR, Dyrda M, Ramanan S, et al. Deep brain stimulation for movement disorders after stroke: A systematic review of the literature. J Neurosurg. 2023;138(6): 1688–1701.
160. Peppe A, Pierantozzi M, Chiavalon C, et al. Deep brain stimulation of the pedunculopontine tegmentum and subthalamic nucleus: Effects on gait in Parkinson's disease. Gait Posture. 2010;32(4):512-518.
161. Pepper J, Hariz M, Zrinzo L, et al. Deep brain stimulation versus anterior capsulotomy for obsessive-compulsive disorder: A review of the literature. J Neurosurg. 2015;122(5):1028-1037.
162. Piacentino M, Durisotti C, Garofalo PG, et al. Anterior thalamic nucleus deep brain stimulation (DBS) for drug-resistant complex partial seizures (CPS) with or without generalization: Long-term evaluation and predictive outcome. Acta Neurochir (Wien). 2015;157(9):1525-1532; discussion 1532.
163. Pichon Riviere A, Augustovski F, Cernadas C, et al. Deep brain stimulation in the treatment of Parkinson's disease. Report IRR No. 9. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); 2003.
164. Pichon Riviere A, Augustovski F, Garcia Marti S, et al. Deep brain stimulation for generalized dystonia treatment. Report IRR No. 40. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); 2005.
165. Pichon Riviere A, Augustovski F, Garcia Marti S, et al. Deep brain stimulation for the treatment of Parkinson's disease [summary]. IRR No. 183. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); 2009.
166. Pinto S, Ozsancak C, Tripoliti E, et al. Treatments for dysarthria in Parkinson's disease. Lancet Neurol. 2004;3(9):547-556.
167. Plaha P, Khan S, Gill SS. Bilateral stimulation of the caudal zona incerta nucleus for tremor control. J Neurol Neurosurg Psychiatry. 2008;79(5):504-513.
168. Plaha P, Patel NK, Gill SS. Stimulation of the subthalamic region for essential tremor. J Neurosurg. 2004;101(1):48-54.
169. Plow EB, Pascual-Leone A, Machado A. Brain stimulation in the treatment of chronic neuropathic and non-cancerous pain. J Pain. 2012;13(5):411-424.
170. Porta M, Brambilla A, Cavanna AE, et al. Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: Two-

year outcome. Neurology. 2009;73(17):1375-1380.

171. Potes MI, Joaquin C, Wiecks N, et al. The utility of deep brain stimulation surgery for treating eating disorders: A systematic review. Surg Neurol Int. 2021;12:169.
172. Rabins P, Appleby BS, Brandt J, et al. Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior, and thought. Arch Gen Psychiatry. 2009;66(9):931-937.
173. Ralph J. Neuroacanthocytosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2021.
174. Raviv N, Staudt MD, Rock AK, et al. A systematic review of deep brain stimulation targets for obsessive compulsive disorder. Neurosurgery. 2020;87(6):1098-1110.
175. Rehncrona S, Johnels B, Widner H, et al. Long-term efficacy of thalamic deep brain stimulation for tremor: Double-blind assessments. Mov Disord. 2003;18(2):163-170.
176. Rezaei Haddad A, Lythe V, Green AL, et al. Deep brain stimulation for recovery of consciousness in minimally conscious patients after traumatic brain injury: A systematic review. Neuromodulation. 2019;22(4):373-379.
177. Richard A, Hsu J, Baum P, et al. Efficacy of deep brain stimulation in a patient with genetically confirmed chorea-acanthocytosis. Case Rep Neurol. 2019;11(2):199-204.
178. Riva-Posse P, Choi KS, Holtzheimer PE, et al. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. Mol Psychiatry. 2018;23(4):843-849.
179. Riva-Posse P, Choi KS, Holtzheimer PE, et al. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2014;76(12):963-969.
180. Rojas-Medina LM, Esteban-Fernandez L, Rodríguez-Berrocal V, et al. Deep brain stimulation in posttraumatic tremor: A series of cases and literature review. Stereotact Funct Neurosurg. 2016;94(6):379-386.
181. Roper JA, Kang N, Ben J, et al. Deep brain stimulation improves gait velocity in Parkinson's disease: A systematic review and meta-analysis." J Neurol. 2016;263(6): 1195-1203.
182. Salanova V, Witt T, Worth R, et al; SANTE Study Group. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015;84(10):1017-1025.

183. Salanova V. Deep brain stimulation for epilepsy. Epilepsy Behav. 2018;88S:21-24.
184. Saleh C, Hasler G. Deep brain stimulation for psychiatric disorders: Is there an impact on social functioning? Surg Neurol Int. 2017;8:134.
185. Sancar F. Deep brain stimulation for tinnitus, tumors hijack neurons in brain cancer, and multiple sclerosis and immunizations: Neuro nook. JAMA. 2019;322(21):2065-2066.
186. Schiff ND. Central thalamic deep brain stimulation to support anterior forebrain mesocircuit function in the severely injured brain. J Neural Transm (Vienna). 2016;123(7):797-806.
187. Schrader C, Benecke R, Deuschl G, et al; German Deep Brain Stimulation Association. Deep brain stimulation for dystonia. Consensus recommendations of the German Deep Brain Stimulation Association. Nervenarzt. 2009;80(6):656-661.
188. Schulz GM, Grant MK. Effects of speech therapy and pharmacologic and surgical treatments on voice and speech in Parkinson's disease: A review of the literature. J Commun Disord. 2000;33(1):59-88.
189. Schulz-Schaeffer WJ, Margraf NG, Munser S, et al. Effect of neurostimulation on camptocormia in Parkinson's disease depends on symptom duration. Mov Disord. 2015;30(3):368-372.
190. Servello D, Zekaj E, Saleh C, et al. Sixteen years of deep brain stimulation in Tourette's syndrome: A critical review. J Neurosurg Sci. 2016;60(2):218-229.
191. Sherry DD. Complex regional pain syndrome in children. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed October 2012.
192. Sirven JI. Evaluation and management of drug-resistant epilepsy. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed September 2018
193. Sobstyl M, Kupryjaniuk A, Mierzejewski P. Nucleus accumbens as a stereotactic target for the treatment of addictions in humans: A literature review. Neurol Neurochir Pol. 2021;55(5):440-449.
194. Sprengers M, Vonck K, Carrette E, et al. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev. 2014;6:CD008497.
195. Starr PA, Turner RS, Rau G, et al. Microelectrode-guided implantation of deep brain stimulators into the globus pallidus

internus for dystonia: Techniques, electrode locations, and outcomes. Neurosurg Focus. 2004;17(1):E4.

196. Starr PA. Placement of deep brain stimulators into the subthalamic nucleus or Globus pallidus internus: Technical approach. Stereotact Funct Neurosurg. 2002;79(3-4):118-145.
197. State of Minnesota, Health Technology Advisory Committee (HTAC). Implantable neurostimulation devices. Technology Assessment Brief. St. Paul, MN: HTAC; September 1998.
198. Stein K. Deep brain stimulation for movement disorders other than Parkinsons disease. STEER: Succint and Timely Evaluated Evidence Reviews. Bazian Ltd., eds. London, UK: Wessex Institute for Health Research and Development, University of Southampton; 2001;1(2):1-10.
199. Tanei T, Kajita Y, Kaneoke Y, et al. Staged bilateral deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Acta Neurochir (Wien). 2009;151(6):589-594.
200. Temel Y, Visser-Vandewalle V. Surgery in Tourette syndrome. Mov Disord. 2004;19(1):3-14.
201. Thase M, Connolly KR. Unipolar depression in adults: Choosing treatment for resistant depression. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2021a.
202. Thase M, Connolly KR. Unipolar depression in adults: General principles of treating resistant depression. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2021b.
203. Thase M, Connolly KR. Unipolar depression in adults: Management of highly resistant (refractory) depression. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2021c.
204. Thase M, Connolly KR. Unipolar depression in adults: Treatment of resistant depression. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2017.
205. The Deep-Brain Stimulation for Parkinson' Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med. 2001;345(13):956-963.
206. Thirunavu V, Du R, Wu JY, et al. The role of surgery in the management of Lennox-Gastaut syndrome: A systematic review and meta-analysis of the clinical evidence. Epilepsia. 2021;62(4):888-907.

207. Timmermann L, Deuschl G, Fogel W, et al; Deep Brain Stimulation Association. Deep brain stimulation for tremor in multiple sclerosis: Consensus recommendations of the German Deep Brain Stimulation Association. Nervenarzt. 2009;80(6):673-677.
208. Tomskiy AA, Poddubskaya AA, Gamaleya AA, Zaitsev OS. Neurosurgical management of Tourette syndrome: A literature review and analysis of a case series treated with deep brain stimulation. Prog Brain Res. 2022;272(1):41-72.
209. Tronnier VM, Fogel W, Kronenbuerger M, et al. Is the medial globus pallidus a site for stimulation or lesioning in the treatment of Parkinson's disease? Stereotact Funct Neurosurg. 1997;69(1-4 Pt 2):62-68.
210. Troster AI, Meador KJ, Irwin CP, et al. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure. 2017;45:133-141.
211. U.S. Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH). Medtronic Activa Dystonia Therapy. Implantable multi-programmable quadripolar deep brain stimulation system. FDA Summary of Safety and Probable Benefit. Humanitarian Device Exemption (HDE) No. H020007. Rockville, MD: FDA; April 15, 2003.
212. U.S. Food and Drug Administration (FDA). FDA approves humanitarian device exemption for deep brain stimulator for severe obsessive-compulsive disorder. FDA News. Rockville, MD: FDA; February 19, 2009.
213. Vanhoecke J, Hariz M. Deep brain stimulation for disorders of consciousness: Systematic review of cases and ethics. Brain Stimul. 2017;10(6):1013-1023.
214. Vannemreddy P, Slavin K. Nucleus accumbens as a novel target for deep brain stimulation in the treatment of addiction: A hypothesis on the neurochemical and morphological basis. Neurol India. 2019;67(5):1220-1224.
215. Vesper J, Chabardes S, Fraix V, et al. Dual channel deep brain stimulation system (Kinetra) for Parkinson's disease and essential tremor: A prospective multicentre open label clinical study. J Neurol Neurosurg Psychiatry. 2002;73(3):275-280.
216. Vesper J, Klostermann F, Wille C, et al. Long-term suppression of extrapyramidal motor symptoms with deep brain stimulation (DBS). Zentralbl Neurochir. 2004;65(3):117-122.

217. Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med. 2005;352(5):459-467.
218. Visser-Vandewalle V, Temel Y, Boon P, et al. Chronic bilateral thalamic stimulation: A new therapeutic approach in intractable Tourette syndrome. Report of three cases. J Neurosurg. 2003;99(6):1094-1100.
219. Visser-Vandewalle V, Temel Y, van der Linden Ch, et al. Deep brain stimulation in movement disorders. The applications reconsidered. Acta Neurol Belg. 2004;104(1):33-36.
220. Voelker R. Electrical stimulation for epilepsy. JAMA. 2018;319(21):2164.
221. Volkmann J, Sturm V, Weiss P, et al. Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. Ann Neurol. 1998;44(6):953-961.
222. Wang JW, Zhang YQ, Zhang XH, et al. Deep brain stimulation of pedunculopontine nucleus for postural instability and gait disorder after Parkinson disease: A meta-analysis of individual patient data. World Neurosurg. 2017;102:72-78.
223. Wang S, Fan S, Gan Y, et al. Efficacy and safety of combined deep brain stimulation with capsulotomy for comorbid motor and psychiatric symptoms in Tourette's syndrome: Experience and evidence. Asian J Psychiatr. 2024;94:103960.
224. Warren AEL, Dalic LJ, Bulluss KJ, et al. The optimal target and connectivity for deep brain stimulation in Lennox-Gastaut syndrome. Ann Neurol. 2022;92(1):61-74.
225. Washington State Department of Labor and Industries. Work-related complex regional pain syndrome (CRPS): Diagnosis and treatment. Olympia, WA: Washington State Department of Labor and Industries; October 1, 2011.
226. Weaver FM, Follett K, Stern M, et al; CSP 468 Study Group. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: A randomized controlled trial. JAMA. 2009;301(1):63-73.
227. Welter M-L, Houeto J-L, Thobois S, et al; STIC study group. Anterior pallidal deep brain stimulation for Tourette's syndrome: A randomised, double-blind, controlled trial. Lancet Neurol. 2017;16(8):610-619.
228. Wilfong A. Lennox-Gastaut syndrome. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2022.

229. Wu H, Van Dyck-Lippens PJ, Santegoeds R, et al. Deep-brain stimulation for anorexia nervosa. World Neurosurg. 2013;80(3-4):S29.e1-e10.
230. Wu Y, Mo J, Sui L, et al. Deep brain stimulation in treatment-resistant depression: A systematic review and meta-analysis on efficacy and safety. Front Neurosci. 2021;15:655412.
231. Wu Y, Xu Y-Y, Gao Y, et al. Deep brain stimulation for chorea-acanthocytosis: A systematic review. Neurosurg Rev. 2022;45(3):1861-1871.
232. Yan H, Toyota E, Anderson M, et al. A systematic review of deep brain stimulation for the treatment of drug-resistant epilepsy in childhood. J Neurosurg Pediatr. 2018;23(3):274-284.
233. Yan S, Yang X, Duan Z. Controlling Alzheimer's disease by deep brain stimulation based on a data-driven cortical network model. Cogn Neurodyn. 2024;18(5):3157-3180.
234. Youngerman BE, Sheth SA. Deep brain stimulation for treatment-resistant depression: optimizing interventions while preserving valid trial design. Ann Transl Med. 2017; 5(Suppl 1): S1. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440297/.
235. Zesiewicz TA, Elbe R, Louis ED, et al. Practice parameters: Therapies for essential tremor. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2005;64(12):2008-2020.
236. Zhou C, Zhang H, Qin Y, et al. A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. Prog Neuropsychopharmacol Biol Psychiatry. 2018a;82:224-232.
237. Zhou JJ, Chen T, Farber SH, et al. Open-loop deep brain stimulation for the treatment of epilepsy: A systematic review of clinical outcomes over the past decade (2008-present). Neurosurg Focus. 2018b;45(2):E5.