

<b>MEDICAL POLICY</b>		<b>Deep Brain and Responsive Cortical Stimulation (All Lines of Business Except Medicare)</b>	
<b>Effective Date: 1/1/2021</b>		Section: SUR	Policy No: 195
 1/1/2021		Medical Policy Committee Approved Date: 11/07; 3/08; 3/10; 2/12; 2/13; 4/14; 8/15; 12/15; 4/16; 5/17; 8/17; 2/18; 12/18; 5/19; 12/19; 12/2020	
Medical Officer	Date		

**See Policy CPT/HCPCS CODE section below for any prior authorization requirements**

**SCOPE:**

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

**APPLIES TO:**

All lines of business except Medicare

**BENEFIT APPLICATION**

Medicaid Members

*Oregon:* Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**POLICY CRITERIA**

**Deep Brain Stimulation**

*Parkinson’s Disease*

I. Deep brain stimulation for the treatment of tremors secondary to Parkinson’s disease may be considered **medically necessary and covered** when **all** of the following (A.-D.) criteria are met:

A. There is clinical documentation of quantifiable testing [e.g., Unified Parkinson Disease Rating Scale (UPDRS)] that indicates the patient is experiencing disabling symptoms of Parkinson’s disease (e.g., motor fluctuations, dyskinesias); **and**

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- B. The patient's symptoms are refractory to optimal medical therapy (e.g., dopaminergic medications); **and**
  - C. The patient does not have dementia and/or any major psychiatric illness; **and**
  - D. The patient has undergone evaluation by a multidisciplinary team and is determined to be an appropriate candidate for deep brain stimulation.
- II. Deep brain stimulation for the treatment of tremors secondary to Parkinson's disease is considered **investigational and is not covered** when criterion I. above is not met.

*Essential Tremor*

- III. Deep brain stimulation for the treatment of essential tremor may be considered **medically necessary and covered** when **all** of the following (A.-C.) criteria are met:
- A. There is clinical documentation of quantifiable testing [e.g., The Essential Tremor Rating Scale (TETRAS)] that indicates the patient is experiencing disabling symptoms of essential tremor; **and**
  - B. The patient's symptoms are refractory to optimal medical therapy (e.g., pharmacological treatments); **and**
  - C. The patient has undergone evaluation by a multidisciplinary team and is determined to be an appropriate candidate for deep brain stimulation.
- IV. Deep brain stimulation for the treatment of essential tremor is considered **investigational and is not covered** when criterion III. above is not met.

*Primary Dystonia*

- V. Deep brain stimulation for the treatment of primary dystonia (including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia) may be considered **medically necessary and covered** when **all** of the following (A.-D.) criteria are met:
- A. The patient is 7 years of age or older; **and**
  - B. There is clinical documentation of quantifiable testing [e.g., The Fahn-Marsden Dystonia Rating Scale (FMDRS)] that indicates the patient is experiencing disabling symptoms of dystonia; **and**
  - C. The patient's symptoms are refractory to optimal medical therapy (e.g., anticholinergic medications); **and**
  - D. The patient has undergone evaluation by a multidisciplinary team and is determined to be an appropriate candidate for deep brain stimulation.

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<p>VI. Deep brain stimulation for the treatment of primary dystonia (including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia) is considered <b>investigational and is not covered</b> when criterion V. above is not met.</p> <p>VII. Deep brain stimulation is considered <b>investigational and is not covered</b> for treating conditions other than those listed above, including, but not limited to, the following:</p> <ul style="list-style-type: none"> <li>• Chronic Pain</li> <li>• Multiple Sclerosis</li> <li>• Epilepsy</li> <li>• Depression</li> <li>• Obsessive Compulsive Disorder</li> <li>• Tourette’s Syndrome</li> </ul> <p><b>Responsive Cortical Stimulation</b></p> <p>VIII. Responsive neurostimulation (RNS) (e.g. NeuroPace) <b>may be considered medically necessary and covered</b> for the treatment of epilepsy when <b>all</b> of the following criteria are met (A.-E.):</p> <ul style="list-style-type: none"> <li>A. Patient is 18 years of age or older; <b>and</b></li> <li>B. Patient has undergone diagnostic testing that localized no more than 2 epileptogenic foci; <b>and</b></li> <li>C. Patient has experienced an average of 3 or more disabling seizures (e.g. motor partial seizures, complex partial seizures and/or secondarily generalized seizures) per month over the prior 3 months; <b>and</b></li> <li>D. Patient’s symptoms are refractory to 2 or more antiepileptic medications; <b>and</b></li> <li>E. Patient is not a candidate for focal resection epilepsy surgery (e.g. have an epileptic focus near eloquent cerebral cortex; have bilateral temporal epilepsy).</li> </ul> <p>IX. Responsive neurostimulation (RNS) (e.g. NeuroPace) is considered <b>investigational and not covered</b> when criterion IX. above is not met.</p> <p>Link to <a href="#">Policy Summary</a></p>
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**CPT/HCPCS CODES**

<b>All Lines of Business Except Medicare</b>	
Prior Authorization Required	
61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical

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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 (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
61864	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
61867	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
61868	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
61880	Revision or removal of intracranial neurostimulator electrodes
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or receiver
95836	Electrocorticogram from an implanted brain neurostimulator pulse generator/transmitter, including recording, with interpretation and written report, up to 30 days
C1767	Generator, neurostimulator (implantable), non-rechargeable
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
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
C1823	Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads
C1883	Adapter/extension, pacing lead or neurostimulator lead (implantable)
C1897	Lead, neurostimulator test kit (implantable)
L8679	Implantable neurostimulator, pulse generator, any type

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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
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

**No Prior Authorization Required**

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 reprogramming
95971	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 spinal cord or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
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

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	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
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)
<b>Unlisted Codes</b>	
All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then <b>prior-authorization is required.</b>	
64999	Unlisted procedure, nervous system

**DESCRIPTION**

**Parkinson’s Disease (PD)**

PD is a progressive, chronic neurodegenerative disorder that affects an estimated 1.5 million Americans.<sup>1</sup> Common symptoms of PD include resting tremor, bradykinesia (slowness of movement), and rigidity. As PD advances it can lead to dementia and death. Currently, there is no cure for PD, but medication and surgical therapy are used to treat its symptoms.<sup>2</sup> Dopaminergic medications (help replenish dopamine in the brain) can reduce muscle rigidity and improve motor function. Surgical therapy of PD includes thalamotomy, pallidotomy, or subthalamotomy, all of which destruct a section of the brain. Deep brain stimulation is another surgical therapy that helps treat PD symptoms while preserving brain structure.

**Essential Tremor (ET)**

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“Essential tremor (ET), a common movement disorder, affects more than 1 million Americans and at least 1% of the adult population over the age of 40 years.”<sup>1</sup> The onset of ET is insidious, commonly in early adulthood, and varies in progression over time. The typical symptoms of ET are a postural tremor of the upper limbs that is absent at rest and not worsened by movement (unlike Parkinson tremor).<sup>3</sup> Currently, there is no cure for ET, but medication and surgical therapy can be used to reduce symptoms. Common pharmacological therapies for ET include the use of propranolol and botulinum toxin injections. Surgical therapies include thalamotomy (destruction/removal of the thalamus) or deep brain stimulation.

**Primary Dystonia**

“Primary dystonia comprises a group of idiopathic, incurable movement disorders that vary with respect to age at onset, body distribution, and genetic association.”<sup>4</sup> Dystonia causes involuntary muscle contractions which results in twisting, repetitive movements or abnormal postures. Currently, there is no cure for dystonia, but medication and surgical therapy are available to help treat the symptoms. Common pharmacological therapies for dystonia include botulinum toxin injections, anticholinergic medications, and muscle relaxants or antispastic agents.<sup>5</sup> The only surgical therapy for dystonia is deep brain stimulation.

**Deep Brain Stimulation (DBS)**

“Deep brain stimulation (DBS) involves constant, high-frequency electrical stimulation of specific sites in the brain with implanted electrodes as a means to reduce the symptoms of movement disorders.”<sup>1</sup> Instead of damaging brain tissue by destroying nerve cells (like thalamotomy, pallidotomy, or subthalamotomy), the DBS device blocks electrical signals from targeted areas of the brain.<sup>6</sup> If needed, this also allows the procedure to be reversed. The DBS device consists of implanted electrodes in the ventral intermediate nucleus (VIM) of the pallidus, internal globus pallidus (Gpi), or subthalamic nucleus (STN) of the brain that are connected to a pulse generator implanted in the chest. After implantation of the DBS device, the stimulation parameters, frequency, pulse width, and voltage can be adjusted to maximize symptom improvement and decrease side effects.

**Responsive Cortical Stimulation**

According to Hayes, “responsive neurostimulation for the treatment of epilepsy involves the use of 1 or more implantable electric leads that serve as seizure monitors (24 hours/day), neurostimulators, and recorders of brain activity for physician review. The device is programmed to recognize seizure patterns from electrocorticography (ECoG) output and to deliver electrical stimulation with the goal of terminating a seizure. Generally, individuals who are candidates for RNS are severely debilitated and have few other treatment options.”<sup>7</sup>

**REVIEW OF EVIDENCE**

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A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of responsive cortical stimulation for the treatment of epilepsy and deep brain stimulation as a treatment for Parkinson’s disease, essential tremor, and dystonia. Below is a summary of the available evidence identified through October 2020.

**Deep Brain Stimulation**

*Parkinson’s Disease (PD)*

Systematic Reviews

- In 2018, Peng and colleagues conducted a systematic review and meta-analysis to evaluate the long-term efficacy of deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) for the treatment of Parkinson’s Disease (PD).<sup>8</sup> Investigators independently searched the literature through 2016, identified eligible studies, assessed study quality, and pooled results. Outcomes of interest were unified PD rating scale section (UPDRS) III off-medication score, PD questionnaire score and levodopa-equivalent dosage after DBS. In total, 5 studies met inclusion criteria and were included for review (n= 890). During the off-medication state, pooled weighted mean difference (WMD) of UPDRS III score was .69 (95% CI =1.77 to 3.16, p =.58). In subgroup analysis, WMD of UPDRS III off-medication scores from baseline to 2 years and 3 years post-DBS were .61 (95% CI=2.97 to 1.75, p =.61) and 2.59 (95% CI=2.30 to 7.47, p =.30). Pooled WMD of changes in tremor, rigidity, and gait scores were 1.12 (95% CI=0.05 to 2.28, p =.06), 1.22 (95% CI=0.51 to 2.94, p =.17) and .37 (95% CI=0.13 to 0.87, P=.15), respectively. After DBS, pooled WMD of PDQ-39 ADL and LED were 3.36 (95% CI=6.36 to 0.36, P=.03) and 194.89 (95% CI=113.16 to 276.63, p <.001). Investigators concluded that both forms of deep brain stimulation improved motor function and activities of daily living for PD, without differences between the two groups.
- In 2018, ECRI assessed the efficacy of three deep brain stimulation systems – Activa neurostimulators,<sup>9</sup> the Infinity DBS System,<sup>10</sup> and the Vercise DBS System.<sup>11</sup> ECRI found that the evidence bases of both Activa neurostimulators and the Vercise DBS System were “somewhat favorable,” whereas data for the efficacy of the Infinity DBS system were “inconclusive.”<sup>12</sup>

For Activa, results from 2 RCTs (n=389) and 3 case series (n=703) reported improvements in symptoms and quality of life. Although serious adverse events were common and some patients’ cognitive decline worsened, ECRI concluded that benefits may outweigh these risks in patients who do not respond to more conservative treatments. ECRI called for additional studies to assess outcomes in patient with early and late symptoms, outcomes beyond 4 years, and comparator groups using other DBS systems. Limited evidence with short-term follow-up (1 RCT, n=160; 1 prospective case series (n=40)) indicated that subthalamic DBS with Vercise improves motor symptoms and quality of life in patients who have had advanced PD for more than 5 years. For the Infinity DBS System, a single RCT (n=136) reported improvements in symptoms but was assessed to be at high risk of bias because investigators and patients were not blinded. Two ongoing studies (n=520) are scheduled for completion in 2020 and may partially address this evidence gap.

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- In 2014, Perestelo-Pérez and colleagues published a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate deep brain stimulation (DBS) in Parkinson’s disease (PD).<sup>13</sup> Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The outcomes of interest were motor function [as assessed by the Unified Parkinson’s Disease Rating Scale-III (UPDRS)], waking time on good functioning without troublesome dyskinesias, levodopa-equivalent dose reduction, medication-induced complications, activities of daily living, health-related quality of life, and neurocognitive and psychiatric effects.

After systematic review, the authors identified 6 RCTs reported in 7 publications that were eligible for inclusion; thus giving a total sample size of 1,184. A total of 5 studies included data on UPDRS-III in the off-medication phase, and all showed a statistically significant effect in favor of DBS. In the on-medication phase, the difference remained statistically significant in favor of DBS. A total of 4 studies assess waking time in good function without troublesome dyskinesias. All studies showed a statistically significant effect in favor of DBS. There were also statistically significant differences between groups in favor of DBS for levodopa-equivalent dose reduction and medication-induced complications. A total of 4 studies assessed activities of daily living and health-related quality of life and all indicated statistically significant effects in favor of DBS. The two studies that evaluated psychiatric effects reported a statistically significant difference in favor of DBS. The results of neurocognitive effects were mixed.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size, contacting study authors for additional information, assessment of heterogeneity, and sensitivity analyses. Limitations were present in the heterogeneity present between studies for some outcomes and the small number of selected studies (possible publication bias). Ultimately, the authors concluded, “Although the number of RCTs obtained is small, the total sample size is relatively large, confirming the efficacy of DBS in the control of motor signs and improvement of patients’ functionality and quality of life. More controlled research is required on the neurocognitive and psychiatric effects of DBS.”<sup>13</sup>

- In 2016, Xie et al. published a multiple-treatments meta-analysis of randomized controlled trials (RCTs) to evaluate the effects of neurostimulation for advanced Parkinson’s disease (PD) patients on motor symptoms.<sup>14</sup> Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The authors aimed to compare internal globus pallidus deep brain stimulation (GPI-DBS) versus subthalamic nucleus deep brain stimulation (STN-DBS) versus medical therapy in advanced PD patients. The outcomes of interest were Unified Parkinson’s Disease Rating Scale scores, quality of life (measured using the PDQ-39 Parkinson’s disease Questionnaire), and medication usage.

After systematic review of the available literature, the authors identified 16 RCTs eligible for inclusion giving a total sample size of 2,186 participants. Based on the randomization and analysis methodology, all studies were deemed to have a low risk of bias. After pooling the data, the authors

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found a significant difference between groups for GPi-DBS compared with medical therapy on the UPDRS score. There was also a significant difference between groups for STN-DBS compared with medical therapy in regards to the UPDRS score. When comparing GPi-DBS with STN-DBS, both had similar efficacy on the UPDRS scores. When comparing GPi-DBS with STN-DBS, results were mixed regarding quality of life and medication usage. Quality of life showed greater improvement in the GPi-DBS patients while STN-DBS appeared to be more effective for medication reduction.

Strengths of this systematic review include the evaluation of literature by independent authors following a pre-defined protocol, the large sample size, assessment of bias inclusion of a large number of studies (reduced publication bias), and the assessment of heterogeneity. Limitations were identified in the heterogeneity observed between some studies and the inclusion of papers only published in English (possible publication bias). The authors concluded, “overall, either GPi-DBS or STN-DBS is an effective technique to control PD patients’ symptoms and improve their functionality and quality of life.”<sup>14</sup>

- In 2016, Tan and colleagues conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacies of globus pallidus (GPi) stimulation and subthalamic nucleus (STN) deep brain stimulation (DBS) for advanced Parkinson’s disease.<sup>15</sup> Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The outcomes of interest were motor and nonmotor function (both measured using the Unified Parkinson’s Disease Rating Scale [UPDRS]), medication usage, neurocognitive and psychiatric effects, and quality of life (QOL).

After systematic review, the authors identified 10 RCTs that were eligible for inclusion; thus producing a total sample size of 1,034 patients. According to the varying follow-up periods of selected RCTs, the authors conducted subgroup analyses at 6, 12, and 24 months postoperatively. No significant difference in the off-medication/on-stimulation phase was found between GPi-DBS and STN-DBS at 6 months follow-up; however, at 12 months a statistically significant effect in favor of GPi-DBS was observed. This significant effect was not observed at 24 months. In the on-medication/on-stimulation phase, the effect was reduced to a non-significant level when GPi-DBS was compared to STN-DBS at 6 months and 12 months; however, STN-DBS showed a statistically significant effect compared to GPi-DBS at 24 months. In regards to levodopa usage, the GPi-DBS group required increased levodopa compared to STN-DBS group. The four studies evaluating depression in DBS patients demonstrated that DBS-STN has a better performance on the depression inventory questionnaire. Results were mixed between studies regarding neurocognitive status. The use of GPi-DBS appeared to be associated with a greater effect in 8 of the 9 subscales of QOL.

Strengths of this study include the systematic review of literature by independent authors following a pre-defined protocol, inclusion of a large number of high quality studies, large sample size, and no language restriction (decrease publication bias). Limitations were present in the heterogeneity present between studies and the short follow-up time (6 months) of some included studies. Ultimately, the authors concluded, “GPi- and STN-DBS significantly improve advanced Parkinson’s patients’ symptoms, functionality, and quality of life.”<sup>15</sup>

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Randomized Controlled Trials (RCTs)

Four RCTs were identified in the review of evidence that evaluated deep brain stimulation for treatment of Parkinson’s disease.<sup>16-19</sup> However, all studies were included in one or more of the systematic reviews described above and will not be reviewed here.

*Essential Tremor (ET)*

Systematic Reviews

- In 2013, Zappia et al. published a systematic review to evaluate treatment options for essential tremor (ET).<sup>20</sup> Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The outcomes of interest were patient motor dysfunction due to tremor severity, adverse events (AEs), and quality of life.

After systematic review, the authors identified 39 studies eligible for inclusion. Of these, there was only one randomized controlled trial (RCT) and the remaining 38 were case series. The one RCT reported statistically significant improvements in disability after 6 months in both thalamotomy and thalamic-DBS; however, thalamic-DBS produced superior results. Several other studies also reported statistically significant disability reduction in the “on state”. Other studies also reported that thalamic-DBS not only reduced limb tremor, but also head and voice tremor. Only one case series evaluated STN-DBS versus thalamic-DBS and reported STN was more effective than thalamic for controlling the long-term treatment of ET (through 9 years of follow-up). Safety events reported in the RCT included 27.5% paresthesias, 18.5% gait or balance disorder, 11% dysarthria, and 10.6% death. It is important to note these safety events included both ET patients and Parkinson’s disease patients and the deaths were not considered a consequence of the surgery.

Strengths of this study included the systematic review of literature by independent authors following a pre-defined protocol, quality assessment of selected studies, and no language restriction (decreased publication bias). However, the poor methodological quality of included studies and the paucity of RCTs was a significant limitation. The authors indicated the lack of RCTs evaluating DBS for ET might be due to ethical reasons. Ultimately, the authors concluded, “thalamic deep brain stimulation is recommended for refractory essential tremor.”<sup>20</sup>

- In 2010, Flora et al. published a systematic review to evaluate deep brain stimulation (DBS) for essential tremor (ET).<sup>21</sup> Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The outcomes of interest were tremor improvement (commonly measured using the Fahn-Tolosa-Marin [FTM] tremor rating scale), adverse events (AEs), and quality of life. After systematic review, a total of 17 studies were identified as eligible for inclusion; thus producing a sample size of 430 patients. The identified studies were analyzed in two separate groups based on how the studies evaluated the treatment effect: outcomes of DBS treatment when stimulation was switched on versus off and outcomes of DBS before and after treatment.

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A total of 12 studies reported outcomes for DBS switched on versus off. All studies indicated a consistently significant improvement when the DBS was switched on compared to off. Out of the 12 studies, 3 followed-up patients for 3 years and all reported continued significant improvements in tremors when the stimulator was turned on versus off. A total of 10 studies also reported improved activities of daily living scores when the DBS was turned on. A total of 5 studies reported outcomes for patients before and after receiving DBS. All studies showed statistically significant improvements in tremor scores after DBS treatment (p-values ranged from P<0.001 to P<0.0001). The study with the longest follow-up also reported significant tremor improvement throughout 27 months. In regards to AEs, most reported events were mild and could be treated by changing the stimulation settings. The most common AEs were paresthesia, dysarthria, and headache. The more severe AEs reported were stroke, syncope, dystonia, lead breakage, and electrode migration.

Strengths of this study include the systematic review of literature by independent authors following a pre-defined protocol, quality assessment of selected studies, and larger sample size. Limitations were identified in the small number of included studies and the limited quality of available evidence. The authors attributed this to the lack of high-quality studies evaluating DBS for ET. The authors concluded, "DBS is possibly a safe and effective therapy for essential tremor."<sup>21</sup>

Randomized Controlled Trials

An RCT was identified in the evidence review that evaluated deep brain stimulation for the treatment of essential tremor.<sup>22</sup> However, this RCT was included in the systematic review described above so it will not be further reviewed.

Nonrandomized Controlled Trials

Two clinical trials reported improvements in tremor, activities of daily living and speech for patients with essential tremor receiving DBS.<sup>23,24</sup> While validity may be limited by small sample sizes (n= 12 to 127), a lack of comparator groups and inadequate follow-up, investigators from both studies concluded that DBS was a safe and effective therapy for patients with severe, medically refractory essential tremors.

*Primary Dystonia*

Systematic Reviews

- In 2019, Cochrane conducted a systematic review evaluating the safety, tolerability and efficacy of deep brain stimulation (DBS) for the treatment of dystonia.<sup>25</sup> Independent investigators systematically searched the literature through May 2018, identified eligible studies, assessed study quality, and extracted data. In total, 2 double-blind, parallel RCTs (n=102) were included for review. The primary outcome of interest was the effect of DBS on the internal globus pallidus nucleus, assessed at 3- and 6-months follow-up.

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Investigators found low-quality evidence at three months that DBS of the internal globus pallidus nucleus may improve overall cervical dystonia-related symptoms (mean difference (MD) 9.8 units, 95% CI 3.52 to 16.08 units), cervical dystonia-related functional capacity (MD 3.8 units, 95% CI 1.41 to 6.19); mood (MD 3.1 units, 95% CI 0.73 to 5.47; 1 RCT, 61 participants) and overall clinical status (MD 2.3 units, 95% CI 1.15 to 3.45). Evidence was inconclusive on whether DBS improved quality of life in cervical dystonia (MD 3 units, 95% CI -7.71 to 13.71; 1 RCT), or emotional state (MD 2.4 units, 95% CI -6.2 to 11.00; 1 RCT).

Studies evaluating DBS of the internal globus pallidus nucleus found low-quality evidence indicating improvements at three months in generalized or segmental dystonia-related symptoms (MD 14.4 units, 95% CI 8.0 to 20.8), overall clinical status (MD 3.5 units, 95% CI 2.33 to 4.67), physical functioning-related quality of life (MD 6.3 units, 95% CI 1.06 to 11.54), and overall dystonia-related functional capacity (MD 3.1 units, 95% CI 1.71 to 4.48). Evidence was inconclusive as to whether DBS improved physical functioning-related quality of life (MD 5.0 units, 95% CI -2.14 to 12.14), or mental health-related quality of life (MD -4.6 units, 95% CI -11.26 to 2.06) in generalized or segmental dystonia. Very low-quality evidence rendered risk of adverse events (RR 1.58, 95% CI 0.98 to 2.54) and tolerability (RR 1.86, 95% CI 0.16 to 21.57) indeterminate.

The overall quality of evidence for neck, limb and trunk dystonia was assessed as ranging from “low to very low.” Investigators concluded that DBS of the internal globus pallidus nucleus may reduce symptom severity and improve functional capacity in adults with cervical, segmental or generalized moderate to severe dystonia and may improve quality of life in adults with generalized or segmental dystonia. Investigators stated that further research with longer follow-up was necessary to better establish treatment safety, tolerability and efficacy.

- In 2019, Ravindran and colleagues conducted a systematic review evaluating and meta-analysis evaluating the safety and efficacy of DBS compared to peripheral denervation for the treatment of cervical dystonia.<sup>26</sup> Independent investigators systematically searched the literature through November 2017, identified eligible studies, assessed study quality, extracted data, and pooled results. In total, 18 articles were included for review, of which 15 studies assessed DBS (n=180) and 3 studies assessed peripheral denervation (n=690). The mean follow-up time was 31.5 months (range: 12 to 38 months). Forest plots revealed significant absolute reduction in total postoperative Toronto Western Spasmoid Torticollis Rating Scale (TWSTRS) scores for both peripheral denervation (MD 1.54; 95% CI 1.42-1.66) and DBS (MD 2.07; 95% CI 1.43-2.71). On subgroup analysis, DBS therapy was significantly associated with improvement in postoperative TWSTRS severity (MD 2.08; 95% CI 1.66-2.50) and disability (MD 2.12; 95% CI 1.57-2.68) but not pain (MD 1.18; 95% CI 0.80-1.55). Study limitations included the largely single-arm or retrospective design, heterogeneous outcome measures, and small sample sizes of most individual studies. Investigators concluded that both peripheral denervation and DBS were associated with significant reduction in TWSTRS total score, but no significant difference between the two. Investigators called for additional, larger trials to better evaluate patient selection criteria and the long-term safety efficacy of DBS.

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- In 2017, Moro and colleagues conducted a systematic review and meta-analysis to evaluate the efficacy of globus pallidus (GPi) deep brain stimulation (DBS) in isolated dystonia.<sup>27</sup> Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The outcomes of interest were improvement in the Bruke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor and disability scores and adverse events.

After systematic review, the authors identified 24 studies eligible for inclusion producing a sample size of 523 patients. The absolute and percentage changes from baseline in the BFMDRS motor and disability scores were pooled. The authors also evaluated associations between treatment effect and patient characteristics (e.g., age) using meta-regression. The mean absolute improvement in BFMDRS motor and disability score at the last follow-up (average 32.5 months) was 26.6 points, and the mean percentage improvement was 65.2%. In regards to disability score at the last follow-up, the mean absolute improvement was 6.4 points and the mean percentage improvement was 58.6%. The multivariate meta-regression analysis did reveal that higher baseline BFMDRS motor and disability scores together with younger age at the time of surgery were associated with significantly better DBS outcomes. Due to inconsistencies in data reporting, the authors could not conduct meta-analysis for the safety outcome.

There were several strengths of this systematic review:

- The gathering of evidence, assessment of quality, and extraction of data by several independent reviewers
- Contacting authors of selected studies for additional information or data
- Assessment of heterogeneity and publication bias
- Meta-analyses only being conducted when studies were determined to be homogeneous with respect to population, treatment, and outcome measures

Study limitations included the low quality of data reported in the available publications; therefore, the authors had to exclude 38% of identified studies leading to potential publication bias. Limitations were also due to discrepancies in reported data and lack of consistency across studies for the safety outcomes. The authors concluded that, “patients with isolated inherited or idiopathic dystonia significantly improved after GPi-DBS.”<sup>27</sup>

### Randomized Controlled Trials (RCTs)

Two RCTs were identified that were not included in the systematic review by Moro et al. described above.

- In 2014, Volkmann et al. published a randomized sham-controlled trial to evaluate pallidal neurostimulation in patients with medication-refractory cervical dystonia.<sup>28</sup> Patients with cervical dystonia were recruited from health care centers in three different countries (Germany, Norway, and Austria). Eligible patients were then randomized 1:1 to receive active neurostimulation (n=32) or sham neurostimulation (n=30) and were postoperatively followed-up at 3 months and 6 months.

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The sham group had the neurostimulator implanted, but the amplitude was set to zero volts. The study was single-blinded, as only the participants were masked to treatment allocation (physician blinding was not possible due to the nature of the procedure and device). The primary outcomes of interest were change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity score from baseline and adverse events (AEs).

A total of 60 patients (97%) had outcome data at 3 months, and 56 patients (90%) had outcome data at 6 months. Statistically significant differences in favor of active neurostimulation were present for reduction in dystonia severity at 3 months ( $P=0.0024$ ). Also at the 3-month follow-up, the TWSTRS severity score improved by 26% in the active neurostimulation group versus 6% in the sham group. At the 6-month follow-up, sham patients had improved by 26% on the TWSTRS severity score since the 3 month follow-up; whereas the active stimulation group only showed minor additional benefit from an extra 3 months of treatment. In regards to AEs, 21 (5 serious) were reported in 11 patients in the active neurostimulation group compared with 20 events (11 serious) in 9 patients in the sham group. The serious AEs were typically related to the implant procedure or the device, and 11 of the 16 were resolved. Common non-serious AEs included dysarthria, involuntary movements, and depression.

Strengths of this study include the randomized controlled design, recruitment from multiple health care centers in different countries, blinding, power analyses, similar characteristics between groups at baseline, and the use of intention to treat analysis. Limitations were identified in the small sample sizes, short follow-up period, and the losses to follow-up. The authors concluded, “pallidal neurostimulation for 3 months is more effective than sham stimulation at reducing symptoms of cervical dystonia. Extended follow-up is needed to ascertain the magnitude and stability of chronic neurostimulation effects before this treatment can be recommended as routine for patients who are not responding to conventional medical therapy.”<sup>28</sup>

- In 2006, Kupsch and colleagues conducted a randomized sham-controlled trial to evaluate pallidal deep brain stimulation in patients with severe primary dystonia.<sup>4</sup> Patients were recruited from 10 academic centers in three different countries (Germany, Norway, and Austria). After surgical implantation of the device, eligible patients were then randomized 1:1 to receive active neurostimulation ( $n=20$ ) or sham neurostimulation ( $n=20$ ) and were postoperatively followed-up at 3 months and 6 months. The sham group had the neurostimulator implanted, but the pulse generator was set to no stimulation. Both the physicians and patients were blinded to treatment allocation. The outcomes of interest were change in the movement score and the effect of neurostimulation on the activities of daily living, the disability score on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), and the quality of life (assessed with the SF-36), and adverse events.

At three months' follow-up, severity scores were statistically significantly lower in the neurostimulation group compared to the sham group ( $P<0.001$ ). The movement score improved by an average of 15.8 points in the neurostimulation group compared to 1.6 points in the sham group. Disability scores also improved significantly in the neurostimulation by an average of 3.9 points versus 0.8 points in the sham group. The neurostimulation group also showed significant

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improvements in quality of life when compared to the sham group (29.8% vs. 11.4%). At 3 months post-operatively, the study became open-label and sham patients were allowed to cross-over. During the open-label period, the improvements in movement, disability, and quality of life were sustained in the neurostimulation group. The sham stimulation group also had similar benefits when they switched to active treatment. At 6 months' post-operative, the combined analysis of all patients indicated substantial improvement in movement, disability, and quality of life when compared to baseline. In regards to safety, 22 AEs occurred in 19 patients. Of these, 5 were severe and were due to infection at the stimulator site (4) and lead dislodgement (1). The most frequent mild adverse event was dysarthria.

Strengths of this study include the randomized controlled design, recruitment from multiple health care centers in different countries, double blinding, power analyses, similar characteristics between groups at baseline, and the use of intention to treat analysis. However, significant limitations were present in the small sample size and short follow-up period. Ultimately, the authors concluded, "bilateral pallidal neurostimulation for 3 months was more effective than sham stimulation in patients with primary generalized or segmental dystonia."<sup>4</sup>

**Investigational Conditions for Deep Brain Stimulation**

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of deep brain stimulation as a treatment for chronic pain, multiple sclerosis, epilepsy, major depressive disorder, obsessive compulsive disorder, and Tourette's syndrome. Below is a summary of the available evidence identified through October 2020.

Chronic Pain

*Systematic Reviews*

In 2019, Frizon and colleagues conducted a systematic review evaluating the efficacy of DBS for intractable pain syndromes.<sup>29</sup> Independent investigators systematically searched the literature through July 2017, identified eligible studies, assessed study quality and extracted data. In total, 22 articles were included for review (n=228; range = 3 to 85), representing results from 17 treatment centers across 6 countries. In included studies, DBS was targeted at either the periaqueductal/periventricular gray matter region, ventral posterior lateral/posterior medial thalamus, or both. The most common pain indications treated were poststroke pain, phantom limb pain, and brachial plexus injury. Outcomes of interest and chronic pain diagnoses varied between studies. Two studies demonstrated significant improvements in quality of life among DBS patients, but no significant reductions in pain scores. The heterogeneity of outcome measures prevented meta-analysis. Other limitations included the lack of specific pain diagnoses among studies and the small sample sizes of individual studies. To substantiate the purported benefits of the therapy, investigators called for standardized outcome measures evaluating success, in addition to further RCTs that focus on a specific, well-defined diagnosis.

*Randomized Controlled Trials*

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In 2017, Lempka and colleagues conducted a double-blind, randomized placebo-controlled RCT evaluating the efficacy of DBS for the treatment of poststroke pain syndrome (PSPS).<sup>30</sup> In total, 9 patients were randomized to active DBS or sham stimulation for 3 months, followed by crossover for another 3-month period. This 6-month blinded phase was then followed by an 18-month open stimulation phase. The primary outcome of interest was a  $\geq 50\%$  improvement on the Pain Disability Index in 50% of patients compared to sham treatment. Results were negative for the primary outcome, although significant improvements in multiple secondary outcome measures were reported (i.e. depression, anxiety and quality of life). Study limitations include the small sample size, lack of long-term follow-up and frequency of serious adverse events (14 events in 9 patients). Investigators concluded that DBS was safe and effective in improving affective components of pain in PSPS patients, although not in reducing disability.

*Nonrandomized Studies*

Two non-systematic literature reviews endorsed the use of DBS for chronic pain conditions patients who have failed medication and conservative care, despite noting a lack of controlled trials, inconsistent results, and unclear patient selection criteria.<sup>31,32</sup>

Multiple Sclerosis (MS)

*Systematic Reviews*

No systematic reviews were identified for the evaluation of DBS for the treatment of tremors in MS patients.

*Randomized Controlled Trials (RCTs)*

In 2017, Oliveira and colleagues conducted a single-blind randomized pilot trial evaluated the safety and efficacy of dual-lead thalamic DBS for the treatment of multiple sclerosis tremor.<sup>33</sup> In total, 12 patients were randomized to receive 3 months of optimized singled-lead DBS, targeting either the ventralis intermedius-ventralis oralis posterior nucleus border (VIM) or the ventralis oralis anterior-ventralis oralis posterior border (VO). Follow-up was 6 months. The primary outcome of interest was mean change in Tolosa-Fahn-Marin Tremor Rating Scale (TRS) scores. Compared with the mean baseline TRS score of 57.0 (SD 10.2), the mean score at 6 months decreased to 40.1 (17.6), -29.6% reduction;  $t=-0.28$ ,  $p=0.03$ . Three of 11 patients did not respond to surgical intervention. Limitations include the study’s small sample size, lack of comparator group receiving sham stimulation, inadequate follow-up, and the lead investigator’s conflict of interest with the device’s manufacturer. Investigators concluded that while dual lead thalamic DBS may improve severe, refractory multiple sclerosis tremor, larger studies with long term follow-up are necessary to establish the therapy’s safety and efficacy.

*Nonrandomized Studies*

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Six nonrandomized studies were identified that evaluated DBS for the treatment of tremors in MS patients.<sup>3,5,6,34-37</sup> All studies were determined to be of poor quality due to their study design (case series), very small sample sizes (n=5 to n=16), short follow-up periods, lack of statistical analysis, and subjective outcome measures.

The results of these studies are conflicting. Four studies suggest DBS may reduce severe, disabling tremors in patients with MS; in contrast, two studies found short-lived tremor reduction and an overall diminished effect of DBS on MS-associated tremors. Only two studies evaluated functional ability after DBS, and both found improvement (one study did not report statistical significance).

Due to the significant methodological limitations of these aforementioned studies, it is difficult to reach conclusions regarding the efficacy of DBS for treating tremors in MS patients. Long-term randomized controlled trials are needed to establish the clinical utility and safety of DBS for tremors secondary to MS.

Epilepsy

*Systematic Reviews*

- In 2019, Hayes conducted a systematic review evaluating the safety and efficacy of deep brain stimulation of the thalamus for treatment of refractory epilepsy.<sup>38</sup> Systematically searching the literature through July 2019, investigators identified 8 studies with results published across 10 publications (2 RCTs, 1 retrospective comparative cohort study, 3 retrospective pretest/posttest studies, 1 registry study and 1 retrospective case series. Samples sizes varied from 11 to 109 patients; follow-up ranged from 1 to 7 years. Outcomes of interest included reduction in seizure frequency, response rates, seizure freedom, seizure severity, quality of life and adverse events.

Results from 2 RCTs comparing active and sham DBS reported mixed findings. One study found significantly greater seizure frequency reduction among patients receiving active DBS, whereas the second study reported no significant differences between groups. Treatment response rate (≥ 50% reduction in seizure frequency) varied considerably, ranging from 22% to 85%. In the largest trial, an RCT with 5-year follow-up, response rates remained as high as 68%. None of the 4 studies assessing freedom from seizures observed patients who achieved complete freedom from seizures over the trial duration, with 3.6% to 5% remaining seizure free for at least 2 years. One RCT reported a significant improvement in QOL during the open-label period through 5-year follow-up. Safety concerns raised in 2 studies included memory loss in a range of 13%-26% of patients, and depression in a range of 15% to 37% of patients, although most participants had a previous history of depression.

The overall strength of evidence supporting findings was assessed as “low.” Generalizability is limited by the lack of well-deigned controlled or comparative studies and the small sample size evaluated in the majority of studies (< 35 in 6 of 8 studies). Hayes ultimately assigned a “C” rating (potential but unproven benefit) for use of DBS in epilepsy patients who have uncontrolled, partial-

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onset seizures (with or without secondary generalization) after  $\geq 3$  antiepileptic drugs. While studies to date have reported durable reductions in seizure frequency, Hayes concluded that “additional well-designed and controlled studies are needed to verify” findings.<sup>38</sup>

- Three recent systematic reviews evaluated the efficacy of DBS for the treatment of medically refractory epilepsy and found mixed results.<sup>39-41</sup> Two studies<sup>39,40</sup> reported significant improvements in seizure frequency, particularly when the anterior nucleus of the thalamus and the hippocampus were stimulated. However, an update to the Cochrane review discussed below,<sup>42</sup> reported that moderate-quality evidence could not demonstrate statistically or clinically significant changes in the proportion of patients who were seizure free after 3 months of treatment.<sup>41</sup> Two of the three studies called for additional, larger RCTs to establish efficacy and optimize treatment parameters.<sup>40,41</sup>
- In 2014, a Cochrane systematic review by Sprengers and colleagues assessed deep brain stimulation (DBS) for epilepsy.<sup>42</sup> Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The outcomes of interest were seizure freedom, responder rate (proportion of patients with at least a 50% seizure frequency reduction compared to baseline), seizure frequency reduction, adverse events, and quality of life.

The authors identified 10 randomized controlled trials (RCTs) comparing intracranial neurostimulation to sham stimulation as eligible for inclusion. Of the selected trials, “one trial was on anterior thalamic DBS (n = 109; 109 treatment periods); two trials on centromedian 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; three trials on cerebellar stimulation (n = 22; 39 treatment periods); three trials on hippocampal DBS (n = 15; 21 treatment periods); and one trial on responsive ictal onset zone stimulation (n = 191; 191 treatment periods).”<sup>42</sup>

There were no statistically significant or clinically significant changes in the proportion of patients who were seizure-free or experienced a 50% or greater reduction in seizure frequency after 1 to 3 months of thalamic DBS, responsive ictal onset zone DBS, and hippocampal DBS. A statistically significant reduction in seizure frequency was identified for anterior thalamic DBS, responsive ictal onset zone DBS, and hippocampal DBS. No significant changes in quality of life were identified for anterior thalamic DBS and responsive ictal onset zone DBS. In regards to safety, electrode implantation resulted in asymptomatic intracranial hemorrhage in 3-4% of patients. Soft tissue infection occurred in 5-13% of patients.

This Cochrane systematic review was of very good quality and had several strengths, including:

1. the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers
2. contacting authors of selected studies for additional information or data

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3. assessment of heterogeneity and publication bias
4. sensitivity analyses to evaluate the influence of studies with a high risk of bias or high losses to follow-up

Limitations of this systematic review include the discrepancies in available data, low methodological quality of some included studies, and the heterogeneity between studies. The authors concluded that more, large and well-designed RCTs are needed in order to validate and optimize the efficacy and safety of invasive intracranial neurostimulation treatments for epilepsy.

*Randomized Controlled Trials (RCTs)*

- In 2017, Cukiert and colleagues conducted an RCT evaluating the efficacy of hippocampal DBS in patients with refractory temporal lobe epilepsy.<sup>43</sup> In total, 16 patients who were refractory to at least three medications were randomized to either active or sham stimulation. Follow-up was 6 months. The primary outcome of interest was  $\geq 50\%$  reduction in seizure frequency. In the active group (n=8), 4 patients became seizure-free; 7 of 8 were considered responders and 1 was a non-responder. Limitations include the small sample size and short-term follow-up. Investigators concluded that hippocampal DBS significantly reduced seizure frequency in the active group compared to the control group, but called for further studies to better define treatment parameters.
- In 2015, Salanova and colleagues reported the long-term safety and efficacy data from their semi-randomized trial evaluating DBS of the anterior nucleus of the thalamus (ANT) for treatment of localization-related epilepsy.<sup>44</sup> The outcomes of interest were seizure frequency, determined using daily seizure diaries, Liverpool Seizure Severity Scale, and quality of life (QOL). Long-term data were available for 110 subjects who experienced at least 6 partial or secondarily generalized seizures per month and who had failed at least 3 antiepileptic drugs. The median percent seizure reduction from baseline was 69% at 5-year follow-up. At 5 years, 68% of patients had  $\geq 50\%$  reduction in seizure frequency, and 16% of subjects were seizure-free for at least 6 months. Limitations include the lack of blinding, lack of comparator group and several authors' conflict of interest with a DBS device manufacturer. Investigators classified results as constituting Class IV evidence (i.e. high risk of bias) that ANT stimulation is associated with a 69% reduction in seizure frequency at 5 years.
- Two additional RCTs were identified in the evidence review that evaluated deep brain stimulation for the treatment of epilepsy.<sup>45,46</sup> However, both studies were included in the systematic review described above so they will not be reviewed further.

Depression

*Systematic Reviews*

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- In 2018, Zhou and colleagues conducted a systematic review and meta-analysis evaluating the efficacy of DBS in patients with treatment-resistant depression (TRD).<sup>47</sup> Independent investigators searched the literature through February 2017, identified eligible studies, assessed study quality, extracted data and pooled results. Outcomes of interest were Hamilton depression rating scale (HDRS) scores and Montgomery-Asberg depression rating scale (MARDS) scores compared at baseline levels and after DBS. In total, 14 studies of DBS were included for review (n= 3 to 25). Interventions targeted the subcallosal cingulate gyrus (SCG), ventral capsule/ventral striatum (VC/VS), medial forebrain bundle (MFB), and nucleus accumbens (NAcc). Investigators reported significant reduction in HDRS in these four regions at up to 12 months’ follow-up. Limitations included the small sample sizes of included studies and inadequate follow-up. Investigators concluded that while DBS may significantly alleviate depressive symptoms in TRD patients, additional larger trials were required to better establish treatment efficacy and patient selection criteria.
- In 2012 (updated 2016; archived 2017), Hayes published an evidence review evaluating the utility of deep brain stimulation (DBS) for treatment-resistant depression (TRD).<sup>48</sup> The review included five studies (all prospective, uncontrolled, open-label studies) evaluating the safety and efficacy of DBS for TRD. Follow-up times ranged from 1 to 6 years and sample sizes varied from 10 to 21 patients, with a total of 86 patients. Outcomes of interest included depressive symptom rating scales, response rate (a 50% reduction in depression scores from baseline), and cognitive function.

The results of 2 studies suggested that DBS in the striatum/nucleus accumbens area improves depressive symptoms. Another study that placed the DBS in the ventral anterior internal capsule/ventral striatum (VC/VS) reported decreased depressive symptoms throughout 12 months’ follow-up. The results of one study also reported reduced depressive symptoms through 48 months in patients that were treated with DBS in the core region of the nucleus accumbens (NAcc), shell region of the nucleus accumbens (NAcSh), ventral anterior internal capsule (VC), and medial internal capsule (MC). Of the selected studies, three reported response rate which varied from 29% to 45%.

Hayes rated the overall quality of evidence to be low due to, “lack of randomization, lack of control/sham or comparator groups, small sample size, lack of blinding, and the financial involvement of the manufacturer of the DBS equipment were all factors limiting the quality of the evidence.”<sup>48</sup> The Hayes review concluded, “there is some evidence that deep brain stimulation (DBS) may reduce depressive symptoms of patients with treatment-resistant depression (TRD), and may increase remission rates. However, the evidence should be considered preliminary since all of the studies lacked a control group, and sample sizes were small across studies. In addition, the manufacturer of the DBS equipment supported most of the studies, and individual authors had financial relationships with the manufacturer in several studies.”<sup>48</sup>

*Randomized Controlled Trials (RCTs)*

No RCTs were identified in the evidence review that evaluated deep brain stimulation for depression. A search of [clinicaltrials.gov](http://clinicaltrials.gov) indicated no new or upcoming RCTs.

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Obsessive Compulsive Disorder (OCD)

*Systematic Reviews*

- In 2020, Vicheva and colleagues published results of a systematic review of DBS for obsessive-compulsive disorder randomized controlled trials.<sup>49</sup> The primary outcomes included Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), adverse events (AE), and quality of life. Amongst 8 studies, 80 patients were evaluated. The authors considered each study individually and pooled data. They reported a pooled mean reduction in Y-BOCS of 38.68 %. Five severe surgery-related AE were identified including intracerebral haemorrhage in three patients and infection in two. Mood-related serious AE were one completed suicide, three suicide attempts in two patients, and suicidal thoughts and depression in four. Given the small samples sizes, additional well designed trials are warranted to fully elucidate the safety and efficacy of DBS for treatment-resistant OCD.
- In May 2018, Hayes conducted a “search and summary” of studies evaluating the efficacy of DBS for the treatment of obsessive compulsive disorder. In total, 12 abstracts were retrieved, including prospective comparative and prospective uncontrolled studies, systematic reviews with and without meta-analyses, cost analyses, a pilot study and a review article. Having assessed the abstracts, Hayes concluded that there was insufficient published evidence to assess the safety and/or impact of DBS on health outcomes or patient management.<sup>50</sup>
- In 2017, Vazquez-Bourgon and colleagues conducted a systematic review evaluating the efficacy of DBS for patients with treatment-resistant obsessive compulsive disorder (OCD). Independent investigators systematically searched the literature through December 2016, identified eligible studies, assessed study quality and extracted data. In total, 20 articles were included for review (n=162). Investigators reported some efficacy of DBS but judged results to insufficient to establish definitive treatment parameters and patient selection criteria. Findings’ validity was further limited by the sample sizes of individual studies included for review (n=2 to 26). Investigators called for additional large, controlled studies with long-term follow-up to further establish efficacy and treatment parameters.<sup>51</sup>
- In 2015, Alonso and colleagues published a systematic review and meta-analysis of treatment outcomes and predictors of response to evaluate deep brain stimulation (DBS) for obsessive compulsive disorder (OCD).<sup>52</sup> Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The outcomes of interest included the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), response rate (a 35% reduction in Y-BOCS scores from baseline), and quality of life.

After systematic review, 31 studies were identified as eligible for inclusion; thus producing a sample size of 116 patients. A total of 83 subjects were implanted in the striatal area, 27 in the subthalamic nucleus, and six in the inferior thalamic peduncle regions of the brain. In regards to the Y-BOCS score changes, 13 studies (n=66 patients) indicated a 45.1% improvement in the DBS patients;

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however, the confidence interval of this parameter was very wide (29.4-60.8%). Data was available from 12 studies to evaluate response rate, and estimated the percentage of responders to be 60%. A total of three studies reported improvement in quality of life in DBS patients; however, this pooled data only included 29 patients.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, inclusion of a large number of studies, and assessment of heterogeneity. However, the validity of this systematic review is severely limited due to significant limitations; including, the poor methodological quality of selected studies (small sample sizes, lack of randomization, and lack of control groups) and the reported heterogeneity between studies. The authors concluded, “well-controlled, randomized studies with larger samples are needed to establish the optimal targeting and stimulation conditions and to extend the analysis of clinical predictors of outcome.”<sup>52</sup>

- Another systematic review and meta-analysis by Kisely et al. (2014) was identified that evaluated deep brain stimulation for treatment of obsessive compulsive disorder.<sup>53</sup> All selected studies were also included in the more recent systematic review described above by Alonso et al.; therefore, it will not be reviewed further.

*Randomized Controlled Trials (RCTs)*

Three RCTs were identified in the evidence review that evaluated deep brain stimulation for the treatment of obsessive compulsive disorder.<sup>54-56</sup> However, all studies were included in the systematic review described above and will not be further reviewed.

Tourette’s syndrome

*Systematic Reviews*

No systematic reviews were identified for the evaluation of DBS for the treatment of Tourette syndrome.

*Randomized Controlled Trials (RCTs)*

In 2017, Welter and colleagues conducted a double-blind RCT evaluating the safety and efficacy of anterior pallidal DBS for the treatment of Tourette’s syndrome (TS).<sup>57</sup> In total, 7 patients received active stimulation and 9 received sham stimulation. No significant difference was noted between groups in the Yale Global Tic Severity Scale at baseline or 3-month follow-up. Notably, 15 serious adverse events occurred in 13 patients. Investigators concluded that 3 months of DBS was insufficient to decrease tic severity, and that future research was needed to establish the efficacy of DBS for patients over longer periods with optimal stimulation parameters.

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*Non-randomized controlled trials*

In 2018, Martinez-Ramirez and colleagues conducted a retrospective cohort study to assess the efficacy and safety of DBS for the treatment of Tourette syndrome across 31 institutions in 10 countries worldwide.<sup>58</sup> Patients with medically refractory symptoms received DBS implantation in the centromedian thalamic region (93 of 163 [57.1%]), the anterior globus pallidus internus (41 of 163 [25.2%]), the posterior globus pallidus internus (25 of 163 [15.3%]), and the anterior limb of the internal capsule (4 of 163 [2.5%]). Among 171 patients (134 males), the mean total Yale Global Tic Severity Scale score improved from 75.01 (18.36) at baseline to 41.19 (20.00) at 1 year after DBS implantation ( $p < .001$ ). The mean (SD) motor tic sub-score improved from 21.00 (3.72) at baseline to 12.91 (5.78) after 1 year ( $p < .001$ ), and the mean (SD) phonic tic sub-score improved from 16.82 (6.56) at baseline to 9.63 (6.99) at 1 year ( $p < .001$ ). The overall adverse event rate was 35.4% (56 of 158 patients), with dysarthria and paresthesia as the most common adverse effects. Study limitations include the use of a multinational registry and database, which included data from all a large, descriptive, unblinded study. The registry also lacks standardized inclusion criteria. While DBS was associated with symptomatic improvement in patients (with important adverse events), investigators called for larger, comparative studies with patients receiving DBS across multiple targets to further refine treatment parameters.

**Responsive Cortical Stimulation**

*Systematic Reviews*

In 2018, ECRI conducted a systematic review evaluating the safety and efficacy of NeuroPace RNS Systems for the treatment of drug-resistant epilepsy.<sup>59</sup> Searching the literature through August 2018, investigators reviewed the texts of two systematic reviews and two case series, as well as the abstract of one nonrandomized comparative study (n=742). Outcomes of interest included seizure frequency, cognitive function, quality of life and adverse events.

One systematic review included the pivotal RCT of the RNS and its single-arm extension (n=191). Investigators reported decreases in Beck’s Depression Inventory I and II scores of 15.2% and 17.9% at 1 and 2 years of follow-up, respectively. For Profile of Mood States (POMS) there was an insignificant decrease of 17.1% between baseline and 1 year but a significant decrease of 20.8% at 2 years. The second systematic review reported that RNS benefits were similar to those achieved by vagus nerve stimulation at 6-year follow-up in both reduction of seizure frequency and quality of life. All randomized controlled trials included in both systematic reviews reported significant reductions in seizure frequency among RNS patients and quality of life. The generalizability of the pivotal RCT, however, may be limited as most patients evaluated suffered specifically from temporal lobe epilepsy.

On the basis on low-to-moderate quality evidence, ECRI concluded the RNS system effectively reduces epileptic seizure frequency at up to 6-year follow-up. Limitations included a lack of RCTs with long-term follow-up, manufacturer conflicts of interest, the lack of studies comparing RNS to both ablative surgery and other neurostimulation approaches to validate long-term RNS benefits and to assess whether these

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benefits translate into QOL improvements. Investigators called for additional comparative studies of RNS and alternative neurostimulation and surgical ablation methods to determine superiority and validate treatment parameters.

*Randomized Controlled Trials*

No randomized controlled trials evaluating the responsive cortical stimulation have been published since ECRI conducted its systematic searches in August 2018. Several RCT's<sup>60-62</sup> were assessed via two systematic reviews as part of the ECRI review.<sup>59</sup>

**EVIDENCE SUMMARY**

Evidence supports the use of deep brain stimulation in patients with severely disabling and refractory Parkinson’s disease, essential tremor, or dystonia. There is not enough evidence to conclude deep brain stimulation is efficacious for the treatment of chronic pain, multiple sclerosis, epilepsy, depression, obsessive compulsive disorder, or Tourette’s syndrome. Future, long-term studies of good methodological quality are required in order to establish the effectiveness and safety of this technology for these conditions. Also, there are no FDA-approved DBS devices indicated for these conditions; therefore, this would be an off-label use of the device.

Evidence from several moderate-quality RCTs indicates that responsive neurostimulation (e.g. NeuroPace) effectively improves patients’ seizure frequency, quality of life and mood at up to 6-year follow-up. While additional comparative studies of RNS are necessary to determine the treatment’s superiority compared to alternative neurostimulation and surgical ablation methods, RNS appears to be an effective option in refractory epilepsy for patients who are not candidates for potentially curative surgery.

**CLINICAL PRACTICE GUIDELINES**

**Responsive Cortical Stimulation**

No relevant clinical practice guidelines were identified addressing the use of responsive cortical stimulation (e.g. NeuroPace) for the treatment of epilepsy.

**Deep Brain Stimulation**

*Parkinson’s disease*

Congress of Neurological Surgeons (CNS)

In 2018, the Congress of Neurological Surgeons (CNS) conducted a systematic review of evidence in support of its guidance on the efficacy of DBS for the treatment of PD.<sup>63</sup> Investigators assessed the

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overall quality of evidence to be “moderate” and concluded that evidence in support of DBS was “mixed” compared to standard care. Despite calling for more research to definitively establish the treatment’s efficacy, CNS recommended DBS for people with advanced PD with symptoms refractory to best medical therapy.

Canadian Agency for Drugs and Technologies in Health (CADTH)

In 2018, the Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review and cost-effectiveness analysis in support of its guidance of the efficacy of DBS for the treatment of PD.<sup>64</sup> Investigators assessed the overall clinical effectiveness findings to be “mixed” and “inconsistent” depending on the outcome examined. CADTH nonetheless concluded that DBS may be a clinically effective means to treat patients with PD.

National Institute for Health and Care Excellence (NICE)

The 2017 NICE evidence-based clinical practice guideline on managing Parkinson’s disease recommended DBS for patients with advanced PD whose symptoms are not adequately controlled by standard care.<sup>65</sup>

American Academy of Neurology (AAN)

The 2006 AAN evidence-based practice parameter for the treatment of Parkinson’s disease with motor fluctuations and dyskinesia stated, “deep brain stimulation (DBS) of the subthalamic nucleus (STN) may be considered to improve motor function and reduce off time, dyskinesia, and medication usage (Level C- possibly effective).”<sup>66</sup> The practice parameter also concluded, “insufficient evidence to support or refute the efficacy of DBS of the globulus pallidus internus (GPi) or ventralis intermedius (VIM) nucleus of the thalamus in reducing off time, dyskinesia, or medication usage, or to improve motor function.”<sup>66</sup>

*Essential Tremor*

American Academy of Neurology (AAN)

The 2005 (revised 2011) AAN evidence-based clinical practice guideline for the treatment of essential tremor (ET) recommended chronic thalamic deep brain stimulation (DBS) of the ventral intermediate nucleus to reduce limb tremor associated with ET (recommendation level C- possibly effective).<sup>67</sup>

*Primary Dystonia*

National Institute for Health and Care Excellence (NICE)

The 2006 NICE evidence-based clinical practice guideline evaluating deep brain stimulation for tremor and dystonia (excluding Parkinson’s disease) stated the, “current evidence on the safety and efficacy of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance.”<sup>68</sup> The guideline also recommended that, “patient selection and

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management should be carried out in the context of a multidisciplinary team specializing in the long-term care of patients with movement disorders.”<sup>68</sup>

*Chronic Pain*

In 2016, the European Academy of Neurology (EAN) conducted a systematic review and meta-analysis in support of its guidelines on central neurostimulation therapy for the treatment of various chronic pain conditions. Having assessed seven case series (n=163), the EAN judged the evidence base for DBS to be “inconclusive.” Limitations in studies to date included studies’ retrospective design, poor selection criteria, heterogeneous methodological approaches and targeted structures. Investigators called for large RCTs to establish efficacy, and define treatment parameters and patient selection criteria.<sup>69</sup>

*Multiple Sclerosis*

No CPGs were identified for the use of DBS in patients with MS.

*Epilepsy*

National Institute for Health and Care Excellence (NICE)

The 2012 NICE evidence-based guideline evaluating deep brain stimulation for refractory epilepsy stated “the evidence on the efficacy of deep brain stimulation (DBS) for refractory epilepsy is limited in both quantity and quality. The evidence on safety shows that there are serious but well-known side effects.”<sup>70</sup>

*Major Depressive Disorder*

American Psychiatric Association (APA)

The 2010 APA evidence-based clinical practice guideline did not provide a recommendation regarding deep brain stimulation for the treatment of major depressive disorder. The guideline stated, “electroconvulsive therapy remains the treatment of best established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared.”<sup>71</sup>

*Obsessive Compulsive Disorder (OCD)*

American Psychiatric Association (APA)

- In 2014, the Congress of Neurological Surgeons conducted a systematic review of evidence in support of their guidance on DBS for the treatment of obsessive compulsive disorder. On the basis of 7 studies, investigators reported that there is Level I evidence for the use of bilateral subthalamic nucleus DBS OCD; Level II evidence for the use of bilateral nucleus accumbens DBS; and insufficient evidence FOR the use of unilateral DBS. Investigators concluded that bilateral DBS is a “reasonable

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therapeutic option” for patients with severe treatment-refractory OCD. Limitations include the conflicts of interest of several investigators with DBS device manufacturers.<sup>72</sup>

- The 2013 APA evidence-based clinical practice guideline for the treatment of patients with obsessive-compulsive disorder stated there are new studies available on deep brain stimulation but the overall strength of evidence for the treatment remains low.<sup>73</sup>

*Tourette’s Syndrome*

European Society for the Study of Tourette Syndrome

In 2011, the European Society for the Study of Tourette Syndrome conditionally endorsed DBS as a “very promising treatment option in adult, treatment resistant, severely affected TS patients,” but called for additional large RCTs to corroborate available results from case studies.<sup>74</sup>

**INSTRUCTIONS FOR USE**

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and PHP Medical Policy will be resolved in favor of the coverage agreement.

**REGULATORY STATUS**

U.S. Food and Drug Administration (FDA)

**FDA-Approved Responsive Cortical Stimulation for Epilepsy**

Device Name	Indications for Use	Contraindications for Use
RNS® System (NeuroPace) <sup>75</sup>	<ul style="list-style-type: none"> <li>• The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to</li> </ul>	<ul style="list-style-type: none"> <li>• Patients at high risk for surgical complications such as active systemic infection, coagulation disorders (such as the use of anti-thrombotic therapies) or platelet count below 50,000.</li> </ul>

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	<p>two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures). The RNS<sup>®</sup> System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.</p>	<ul style="list-style-type: none"> <li>• Patients who have medical devices implanted that deliver electrical energy to the brain.</li> <li>• Patients who are unable, or do not have the necessary assistance, to properly operate the NeuroPace<sup>®</sup> Remote Monitor or Magnet.</li> <li>• The following medical procedures are contraindicated for patients with an implanted RNS<sup>®</sup> System. Energy from these procedures can be sent through the implanted brain stimulation system and cause permanent brain damage which may cause severe injury, coma, or death. Brain damage can occur from any of the listed procedures even if the RNS<sup>®</sup> Neurostimulator is turned off or if the Leads are not connected to the Neurostimulator, and can occur even if the Neurostimulator has been removed, if any Leads (or any part of a Lead), or the cranial prosthesis remain.</li> </ul> <p>- MR imaging is contraindicated for patients with an implanted RNS<sup>®</sup> System. Do not perform an MRI on a patient with any implanted RNS<sup>®</sup> Neurostimulator or Lead (or any portion of a Lead). Even if the Neurostimulator has been removed, the patient should not have an MRI if any part of a Lead or the Cranial Prosthesis is still implanted. The RNS<sup>®</sup> System is MR Unsafe. Testing has not been performed to define conditions of use to</p>
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		<p>ensure safety of the RNS<sup>®</sup> System in an MR environment.</p> <ul style="list-style-type: none"> <li>- Diathermy procedures are contraindicated in patients implanted with an RNS<sup>®</sup> Neurostimulator and associated Leads. (Diathermy is any treatment that uses high-frequency electromagnetic radiation, electric currents, or ultrasonic waves to produce heat in body tissues.) Patients absolutely CANNOT be treated with any type of shortwave, microwave, or therapeutic ultrasound diathermy device whether or not it is used to produce heat. These treatments should not be applied anywhere on the body.</li> <li>- Electroconvulsive Therapy (ECT) is contraindicated for patients with an implanted RNS<sup>®</sup> System.</li> <li>- Transcranial Magnetic Stimulation (TMS) is contraindicated for patients with an implanted RNS<sup>®</sup> System.</li> </ul>
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**FDA-Approved Deep Brain Stimulation Devices for Parkinson’s Disease and Essential Tremor**

A search of the U.S. Food & Drug Administration (FDA) Medical Devices Database identified two FDA-approved DBS devices for Parkinson’s disease and essential tremor:

Device Name	Indications for Use	Contraindications for Use
Activa <sup>®</sup> Tremor Control System	<ul style="list-style-type: none"> <li>• Unilateral thalamic stimulation for the suppression of tremor in the upper extremity in patients who are</li> </ul>	<ul style="list-style-type: none"> <li>• Patients who are unable to operate the system</li> </ul>

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<p>by Medtronic, Inc.<sup>76</sup></p>	<p>diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medication and where the tremor constitutes a significant functional disability.</p>	<ul style="list-style-type: none"> <li>• Patients who have unsuccessful test stimulation</li> <li>• The following procedures are contraindicated for patients with DBS <ul style="list-style-type: none"> <li>○ Diathermy</li> <li>○ Electroshock therapy and transcranial magnetic stimulation</li> </ul> </li> <li>• <b>Not MRI compatible</b></li> </ul>
<p>Brio Family of Deep Brain Stimulation Systems</p> <p>by St. Jude™ Medical<sup>77</sup></p>	<ul style="list-style-type: none"> <li>• Bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinson’s disease that is not adequately controlled by medications.</li> <li>• Unilateral or bilateral stimulation of the ventral intermediate nucleus (VIM) of the thalamus for the suppression of disabling upper extremity tremor in adult essential tremor patients whose tremor is not adequately controlled by medications and where the tremor constitutes a significant functional disability.</li> </ul>	<ul style="list-style-type: none"> <li>• Patients who are unable to operate the system</li> <li>• Patients who have unsuccessful test stimulation</li> <li>• The following procedures are contraindicated for patients with DBS <ul style="list-style-type: none"> <li>○ Diathermy</li> <li>○ Electroshock therapy and transcranial magnetic stimulation</li> </ul> </li> <li>• <b>Not MRI compatible</b></li> </ul>
<p>Vercise Deep Brain Stimulation (DBS) System</p> <p>by Boston Scientific Corporation<sup>78</sup></p>	<ul style="list-style-type: none"> <li>• Bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of moderate to advanced levodopa-responsive Parkinson’s disease that are not adequately controlled with medication</li> </ul>	<ul style="list-style-type: none"> <li>• Patient Incapability</li> <li>• Poor Surgical Candidates</li> <li>• Unsuccessful Test Stimulation</li> <li>• The following procedures are contraindicated for patients with DBS: <ul style="list-style-type: none"> <li>○ Diathermy</li> <li>○ Electroshock therapy and transcranial magnetic stimulation</li> <li>○ Magnetic Resonance Imaging (MRI)</li> </ul> </li> </ul>

**FDA-Approved Deep Brain Stimulation Device for Dystonia:**

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The Activa® Dystonia Therapy System (Medtronic, Inc.) is the only FDA-approved deep brain stimulation device for dystonia.<sup>79</sup>

Device Name	Indications for Use	Contraindications for Use
Activa® Dystonia Therapy System by Medtronic, Inc.	<ul style="list-style-type: none"> <li>Unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.</li> </ul>	<ul style="list-style-type: none"> <li>Patients who are unable to operate the system</li> <li>Patients who have unsuccessful test stimulation</li> <li>The following procedures are contraindicated for patients with DBS <ul style="list-style-type: none"> <li>Diathermy</li> <li>Electroshock therapy and transcranial magnetic stimulation</li> </ul> </li> <li><b>Not MRI compatible</b></li> </ul>

The Activa® Dystonia Therapy System received approval in 2003 under the Humanitarian Device Exemption (HDE) process.<sup>80,81</sup>

HDE is a special FDA approval that allows a device to be marketed on a limited basis provided that:

- The device is used to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year
- The device would not be available to a person with such a disease or condition unless the exemption is granted
- No comparable device is available to treat or diagnose the disease or condition; and
- The device will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment

HDE applications are not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury. The labeling must also indicate that the effectiveness of the device for the specific indication has not been demonstrated.

Humanitarian use devices may only be used in facilities that have obtained an institutional review board (IRB) approval to oversee the usage of the device in the facility, and after an IRB has approved the use of the device to treat or diagnose the specific rare disease. The HDE holder (defined as the person who or entity that obtains the approval of an HDE from FDA) is responsible for ensuring that a device approved

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under an HDE is administered only in facilities having an IRB constituted and acting in accordance with the FDA’s regulation governing IRBs (21 CFR Part 56), including continuing review of use of the device.

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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