DBS FACT SHEET

Medtronic DBS Therapy for Parkinson's Disease, Tremor, Dystonia, and Epilepsy

Medtronic

Parkinson's Disease (PD)

Parkinson's is a neurodegenerative disease. Movement is normally controlled by dopamine, a chemical that carries signals between the nerves in the brain. When cells that normally produce dopamine die, the symptoms of Parkinson's appear. [i]

MOST COMMON SYMPTOMS:

- Tremor
- Slowness and stiffness
- Impaired balance
- Rigidity of the muscles

OTHER SYMPTOMS:

- Fatigue
- Soft speech
- Problems with handwriting
- Stooped posture
- Constipation
- Sleep disturbances

Treatment Options for Parkinson's Disease (PD)

PD is a disease of the central nervous system. It is progressive, which means that symptoms get worse over time. Medications and surgical treatments may control movement symptoms of PD. Physical Therapy can also help. Treatment typically starts with medication. Medications may help reduce movement symptoms by increasing dopamine in the brain or mimicking its effects. Surgical options include DBS, levodopa-carbidopa intestinal pump, pallidotomy and thalamotomy.

The Medtronic Deep Brain Stimulation (DBS) System for PD is bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

Medtronic's DBS System obtained first CE Mark and Health Canada license for advanced PD in 1998 and FDA approval in 2002. Since 1987, more than 175,000 patients worldwide have received Medtronic DBS Therapy.[ii]

What results can be expected from DBS therapy for Parkinson's Disease (PD)?

Below is a summary of the first Level I randomized controlled trial of Medtronic DBS Therapy for Parkinson's disease that examines the impact of the therapy in patients with recent onset motor complications. The study is also the first to compare Medtronic DBS Therapy to best medical therapy (BMT) out to 24 months.[iii]

MOTOR FUNCTION:

DBS (STN) patients with recent onset of motor complications achieved a 20% statistically significant improvement in time with good mobility and no troublesome dyskinesia (2.1 hours from baseline) compared to 2% (0.2 hours) with BMT alone at 24-month follow-up. "On" time without troublesome dyskinesia at baseline was 10.3 hours. [iii]

In an off-medication condition, DBS therapy shows improvement (of at least 5 points in the UPDRS III). DBS improves 89% from baseline to 6 months compared to 37% in the patients with BMT alone in the study of patients with longer-standing motor complications. 83% of STN patients and 74% of GPi patients improve from baseline to 24 months.

QUALITY OF LIFE:
DBS improved PD related QOL by 20.6% vs. BMT at 6 months, and 12.6% STN and 12.5% GPI at 24 months as compared to baseline.

SAFETY:
Overall serious adverse events (SAE) affected 56.5% of the STN patients and 51.0% of GPi patients in the Level 1 evidence clinical study of patients with longer-standing complications at 24 months.

99% of the serious adverse events are resolved at six months with or without sequelae.

What research has been done on Brain State?

Brain state sensing research began in 2013 using the Medtronic Activa™ PC+S system. The Activa™ PC+S system is an investigational system used for research related to brain state sensing; it is not licensed by Health Canada for commercial use. The following statements summarize evidence based on sensing local field potentials (LFPs) in research studies:[1]

- In patients with PD demonstrated to have measurable LFP signals in the beta band, those signals may be present and measured not only immediately following implant, but also for years post-implant.[iv,v,vi, vii, viii]
- Some publications suggest that LFP power measurements at select frequencies taken in-office in certain subgroups of PD patients may correlate to patient's symptomatic state, patient's medication state (on or off PD meds), and level of DBS stimulation.[iv, ix, x, xi, xii, xiii, xiv]
- Elevated LFP power in beta band within STN may correlate with some clinical symptoms of patients with PD having predominantly akinetic-rigid symptoms as measured in office. [iv, xiii, xiv, xv, xvi]

[1] Signals may not be present or measurable in all patients. Clinical benefits of brain sensing have not been established.

Why is DBS therapy an important addition to the treatment continuum for Parkinson's Disease (PD)?

DBS Therapy for Parkinson's disease is an important addition to the treatment continuum because:

- Parkinson's disease may have a significant impact on a patient's quality of life.
- The therapy has been studied in 5 large randomized control trials. [iii, xvii, xviii, xix, xx, xxi]
- Unlike other DBS manufacturers, Medtronic DBS systems are full body[2] MR Conditional at 1.5T and 3T. Activa systems (1.5T) Percept System (1.5 and 3T).
- BrainSense™ Technology may be used to gather objective, personalized information on patients' disease status, inside and outside of the clinic.[3]
- Medtronic Percept™ PC Neurostimulator with BrainSense™ Technology is the only DBS system to chronically capture and record signals from the brain.[3]

Epilepsy

Epilepsy is a brain disorder that produces abnormal bursts of electrical activity in the brain. If uncontrolled, it results in recurrent seizures that vary in:

Frequency: Less than 1 per year to many per day
Form: Different symptoms and signs
Duration: A few seconds to a few minutes or longer

Canadians living with epilepsy can experience different health and social consequences. With the right care, it is possible to manage epilepsy and limit or even prevent seizures. About 300,000 Canadians are living with epilepsy.[4]

The Medtronic Deep Brain Stimulation (DBS) System for Epilepsy is indicated as bilateral stimulation of the anterior nucleus of the thalamus (ANT) as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures (seizures originating from one cerebral hemisphere), with or without secondary generalization (spreading to the other hemisphere), that are refractory to three or more antiepileptic medications.
The DBS system has demonstrated safety and effectiveness in patients who averaged six or more seizures per month over the three most recent months prior to system implant (with no more than 30 days between seizures).
The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures. Health Canada approved Medtronic's DBS System for Epilepsy on March 15, 2012. This therapy is similar to DBS for Parkinson's disease and DBS for essential tremor, for example, implantable components for epilepsy are also indicated for

[2] Medtronic DBS systems are MR Conditional and safe in the MR environment as long as certain conditions are met. If the conditions are not met, a significant risk is tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death. Refer to the MRI Guidelines for Medtronic Deep Brain Stimulation Systems for a complete list of conditions http://professional.medtronic.com/mri

[3] Signals may not be present or measurable in all patients. Clinical benefits of brain sensing have not been established.

[4] https://www.canada.ca/en/public-health/services/publications/diseases-conditions/epilepsy.html

	Parkinson's disease and essential tremor. Since 1987, more than 175,000 patients worldwide have received Medtronic DBS Therapy.
What are the treatment options for Epilepsy?	Guidelines recommend that adults with drug-resistant epilepsy be evaluated for their suitability for resective surgery (the removal of brain tissue using either an open procedure or laser-guided strategy). However, resective surgery is not an option for all patients. For drug-resistant epilepsy patients who are ineligible for, or refuse resective surgery, neurostimulation alternatives include DBS, Vagus Nerve Stimulation (VNS) and Responsive Neurostimulation (RNS).
What results can be expected from DBS therapy for Epilepsy?[xxii]	▪ In Medtronic's randomized controlled clinical trial called "SANTÉ" (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy), the long-term safety and effectiveness for DBS Therapy for Epilepsy was established through 2–7 years.[xxiii, xxiv, xxv, xxvi] ▪ At the end of the 3-month blinded phase of the study (final month), the median total seizure frequency reduction from baseline was 40.4% versus 14.5% for the placebo group. In addition, DBS significantly reduced patients' most severe seizures, complex partial seizures, and the incidence of epilepsy-related injury.[xxii, xxiii] ▪ At year 7, patients experienced a median 75% reduction in seizure frequency from baseline, as assessed with open-label ongoing therapy. Seventy-four percent of patients were considered responders to DBS therapy and had experienced at least a 50% reduction in their seizures. Eighteen percent of patients were seizure-free for at least 6 consecutive months at any time between implant and year 7. Further, there were significant improvements in seizure severity and quality of life. Long- term, there was an improvement in seizure frequency from baseline in patient subgroups whom had tried VNS or had a prior resective surgery.[xxiv] ▪ No significant cognitive declines or worsening of depression scores were observed through the blinded phase or in open- label at 7-years. Higher scores were observed at 7 years on measures of executive functions and attention.[xxvi] ▪ Assessment of long-term safety, based on a minimum of 7 years of follow-up for all subjects active in the study, indicated the rate of intracranial hemorrhages (ICH) Serious Adverse Events (SAEs) was 0.9%, and resolved without sequelae or surgical intervention. Device-related intracranial hemorrhages were asymptomatic. The most frequent device-related SAEs were implant site infection (10.9%) and lead(s) not within target (8.2%), with all others reported in 1.8% of subjects or fewer. The majority of the device-related SAEs occurred during the Operative Phase. The SUDEP rate (2.5 per 1000 person-years) was not elevated compared to the rate reported in a similar patient population of epilepsy surgical candidates.[xxvii] ▪ Overall, the clinical profile for DBS Therapy for Epilepsy demonstrates long-term improvements in epilepsy-related clinical symptoms, with 84% of

	patients (54/64) indicating they were satisfied or greatly satisfied with the results after 7 years.
Why is DBS therapy important to the Epilepsy treatment continuum?	DBS Therapy for Epilepsy is important to the treatment continuum because: ▪ Epilepsy may have a significant impact on a patient's quality of life. ▪ The therapy has been studied in a randomized controlled trial providing Class 1 evidence. ▪ Medtronic DBS systems are MR Conditional and are safe for MRI scans under certain conditions.[2] ▪ Medtronic DBS therapy does not require the seizure foci to be identified for patients with focal (partial-onset) seizures. ▪ Only 10-20% of the people with refractory epilepsy are good candidates for resective surgery; therefore, alternative treatment options such as DBS are needed.[xxviii]
Dystonia[5] and Tremor	The Medtronic Deep Brain Stimulation (DBS) System for dystonia is unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) indicated as an 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. More than 175,000 patients worldwide have received from Medtronic DBS Therapy.[6]
What are the treatment options for dystonia?	Dystonia is a neurological movement disorder characterized by involuntary muscle contractions. These contractions force certain parts of the body into repetitive, twisting movements or painful postures that may interfere with everyday functions like walking, sleeping, eating, and talking. Although dystonia has no cure, there are several treatments such as medication and injections, drug therapies, rhizotomy and pallidotomy, and DBS therapy.
Safety and Probable Benefit of DBS Therapy[xxix, xxx]	The safety and probable benefit of DBS Therapy for dystonia is approved by the FDA under a Humanitarian Device Exemption (HDE). The therapy delivers stimulation to targeted areas of the brain that may decrease some or all symptoms. Symptoms will return when the stimulation is turned off. During DBS Therapy, a small, pacemaker-like device sends electrical signals to an area in the brain that controls movement. These signals block some of the brain messages that cause frustrating and disabling motor symptoms. The device is placed under the skin in the chest (or abdomen). Very thin wires connect the device to the brain to enable the signals to reach the source of symptoms. Most people don't feel the stimulation at all as it reduces their symptoms. Some people may feel a brief

[5] **Humanitarian Device:** The effectiveness of the devices for the treatment of dystonia has not been demonstrated.

[6] Based on sales information dated January 2020 and includes the following indications; Parkinson's disease, essential tremor, obsessive-compulsive disorder, dystonia, and epilepsy.

tingling when the stimulation is first turned on. Following the procedure, stimulation settings are adjusted by the physician to manage individual symptoms.

The physician may provide the patient with a small hand-held programmer to adjust stimulation within physician set limits and turn the device on and off. Over time, settings can be adjusted by physicians as symptoms change. A few weeks after the procedure, people can go back to normal daily activities following their physician's instructions.

The stimulation targets used in DBS Therapy for dystonia as well as the implant procedure are the same as for DBS Therapy for Parkinson's disease and DBS Therapy for essential tremor. Therefore, risks associated with DBS Therapy for dystonia are similar to risks associated with DBS Therapy for Parkinson's disease or essential tremor.

DBS Therapy is not for everyone. DBS Therapy requires brain surgery which can have serious and sometimes fatal complications. Other complications can occur and may require additional surgery. DBS Therapy may cause new or worsening neurological or psychiatric symptoms. In patients receiving DBS Therapy for dystonia, depression, suicidal ideations, and suicide have been reported, although no direct cause-and-effect relationship has been established. Onset of status dystonicus, which may be life-threatening, may occur in dystonia patients during ongoing or loss of DBS Therapy.

Why is DBS therapy important to the treatment continuum?

Dystonia is a challenging disease complex to treat because the various pathophysiologies leading to the disease conditions are not well understood. No cures and no treatments exist to reverse the course of the disorder. Medtronic DBS therapy for patients with dystonia is considered advantageous because:3[xxxi]

- treatment is reversible (device can be turned off or removed)
- stimulation parameters are adjustable for optimal therapy; and
- DBS therapy is non-destructive, an especially important feature in a developing brain because it does not foreclose the possibility for future therapeutic interventions.

Unlike other DBS manufacturers, Medtronic DBS systems are full-body MR Conditional** at 1.5T and 3T. Activa systems (1.5T) Percept Systems (1.5 and 3T).

The probable benefit to health from the use of Medtronic DBS therapy for dystonia outweighs the risk of injury or illness from its use.

Brief Statement: Medtronic DBS Therapy for Parkinson's Disease, Tremor, Dystonia, and Epilepsy

Medtronic DBS Therapy for Parkinson's Disease, Tremor, Dystonia, and Epilepsy: Product labeling must be reviewed prior to use for detailed disclosure of risks.

INDICATIONS:

Medtronic DBS Therapy for Parkinson's Disease: Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Parkinson's Disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

Medtronic DBS Therapy for Tremor: Unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) using Medtronic DBS Therapy for Tremor is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

Medtronic DBS Therapy for Dystonia*: Unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Dystonia is indicated as an 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.

Medtronic DBS Therapy for Epilepsy: Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

CONTRAINDICATIONS: Medtronic DBS Therapy is contraindicated (not allowed) for patients who are unable to properly operate the neurostimulator and, for Parkinson's disease and Essential Tremor, patients for whom test stimulation is unsuccessful. The following

procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if they have an implanted Soletra™ Model 7426 Neurostimulator, Kinetra™ Model 7428 Neurostimulator, Activa™ SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.

WARNINGS: There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths. Extreme care should be used with lead implantation in patients with a heightened risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as cardiac pacemakers or therapies, cardioverter/defibrillators, external defibrillators, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious and permanent injury including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants ("abandoned systems"); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. Cessation, reduction, or initiation of stimulation may potentially lead to an increase in seizure frequency, severity, and new types of seizures. Symptoms may return with an intensity greater than was experienced prior to system implant, including the potential for status epilepticus. Depression, suicidal ideations and suicide have been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause-and-effect relationship has been established. Preoperatively, assess patients for depression and carefully balance this risk with the potential clinical benefit. Postoperatively, monitor patients closely for new or changing symptoms of depression and manage these symptoms appropriately. Patients should be monitored for memory impairment. Memory impairment has been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause-and-effect relationship has been established. The consequences of failing to monitor patients are unknown. When stimulation is adjusted, monitor patients for new or increased seizures, tingling sensation, change in mood, or confusion. Patients should avoid activities that may put undue stress on the implanted components of the neurostimulation system. Activities that include sudden, excessive or repetitive bending, twisting, or stretching can cause component fracture or dislodgement that may result in loss of stimulation, intermittent stimulation, stimulation at the fracture site, and additional surgery to replace or reposition the component. Patients should avoid manipulating the implanted system components or burr hole site as this can result in component damage, lead dislodgement, skin erosion, or stimulation at the implant site. Patients should not dive below 10 meters (33 feet) of water or enter hyperbaric chambers above 2.0 atmospheres absolute (ATA) as this could damage the neurostimulation system, before diving or using a hyperbaric chamber, patients should discuss the effects of high pressure with their clinician.

PRECAUTIONS: Loss of coordination in activities such as swimming may occur.

ADVERSE EVENTS: Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy and weight gain or loss.

The safety and effectiveness of this therapy has not been established for patients without partial-onset seizures, patients who are pregnant or nursing, patients under the age of 18 years, patients with coagulopathies, and patients older than 65 years. USA

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[i] https://www.parkinson.ca/about-parkinsons/understanding-parkinsons/

[ii] Based on sales information dated January 2020 and includes the following indications; Parkinson's disease, essential tremor, obsessive-compulsive disorder, dystonia, and epilepsy.

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