

CADTH Horizon Scan

Adaptive Deep Brain Stimulation for the Treatment of Parkinson Disease and Essential Tremor

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Key Messages

- Horizon Scan reports provide brief summaries of information regarding new and emerging health technologies; *Health Technology Update* articles typically focus on a single device or intervention.
- These technologies are identified through the CADTH Horizon Scanning Service as topics of potential interest to health care decision-makers in Canada.
- This Horizon Scan summarizes the available information regarding an emerging technology, Percept PC Deep Brain Stimulation (DBS) system with BrainSense technology, for the treatment of Parkinson disease and essential tremors.

Percept PC: A New Frontier for Deep Brain Stimulation Adaptability in the Treatment of Parkinson Disease and Essential Tremors

Deep brain stimulation (DBS) is an invasive neurosurgical therapy for patients with movement disorders such as Parkinson disease, essential tremor, and dystonia whose symptoms are inadequately controlled with usual therapies.^{1,2} Other indications for DBS include depression, obsessive-compulsive disorder, Tourette syndrome, epilepsy, cluster headache and chronic pain, including pain from stroke, amputation, trigeminal neuralgia, and multiple sclerosis.³ The procedure involves implanting electrodes in the brain to deliver electrical stimulation using an implanted battery source called an impulse generator.¹ DBS is known to induce biological changes, such as neurophysiological, neurochemical, neurovascular, neurogenic, and neuro-oscillatory effects. However, the exact mechanism by which it works to improve movement disorders is unclear.⁴ Proposals put forward to explain the effects of DBS include the inhibition hypothesis and the jamming hypothesis. The inhibition hypothesis proposes that DBS exerts a dampening effect on overactive neurons, whereas the jamming hypothesis suggests that DBS disrupts communication pathways, including reversing the direction of the brainwaves (i.e., induction of antidromic excitation in afferent axons).⁴

In a traditional DBS procedure, a neurologist programs the stimulation parameters after a surgeon has placed stimulating electrodes in the brain targeting the part of the brain associated with the disorder. The locations of the electrodes' targets are determined using preoperative imaging techniques.⁵ Based on microelectrode recording, patient-reported baseline stimulation effects, and the neurologist's experience, both of which are subjective, the neurologist selects pulse-width, current or voltage amplitude, and frequency of the stimulation to control patients' symptoms while minimizing over-stimulation that may lead to undesirable side effects.⁵ Standard DBS is delivered continuously, and adjustments are made manually by a trained clinician based on a patient's changing symptoms.⁶ This means that patients may be exposed to unnecessary intensive energy that may result in stimulation-induced side effects.^{5,6} Thus, a more objective approach to detect and analyze patient-specific biomarkers and adjust stimulation based on the responses of these biomarkers could enhance the therapeutic benefit of DBS while minimizing side effects. The Percept PC is the first authorized DBS device capable of delivering electrical stimulations while recording electrophysiological changes at the target location in the brain.^{5,7} Percept PC is an adaptive DBS (aDBS) device, meaning it can deliver electrical stimulations based on fluctuations of the brain signals (local field potential [LFP]) at the target structure.⁷

How It Works

Abnormal brain electrical activity (i.e., abnormal brainwave), represented by specific frequency bands, have been identified as electrophysiological biomarkers in patients with movement disorders.⁵ For example, Parkinson disease is correlated with oscillations in the beta power band (8 Hz to 30 Hz) in the subthalamic nucleus (STN),^{1,2,5,8,9} whereas essential tremor correlates with theta-alpha oscillations (4 Hz to 14 Hz) within the ventral intermediate nucleus of the thalamus (VIM).^{5,8,10,11}

The general outlay of Percept PC is like other DBS systems, consisting of DBS electrodes, extension wires, and an implantable pulse generator (IPG) (Figure1).² The IPG (also called neurostimulator), powered by a hybrid silver vanadium oxide battery, generates an electric current that travels through the extension wire to the DBS electrodes, placed to effect stimulation at a set frequency in a specific location in the brain responsible for the disease symptoms.^{2,5} The system can be configured to work within and outside a clinic. Signals can

Figure 1: Percept PC Neurostimulator



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be surveyed and streamed continuously in the clinic, and the device can be programmed to record signals of interest continuously outside of the clinic across a 60-day timeline. The system can be connected to a user interface, such as a clinician programming tablet, communicator, and a patient controller. The setup allows the time-matching of signal changes to patient-recorded events that occur outside the clinic, such as inability to move in a normal way (dyskinesia), tremor, and rigidity.⁵ Thus, Percept PC facilitates condition-dependent stimulation and records symptom-related changes that may provide new insights into the pathophysiological mechanisms of a disease.⁷ Therefore, the device would allow the clinician to track patient-specific biomarkers over time and individualize DBS treatment for improved patient outcomes.⁵

Like other DBS devices, the Percept PC delivers high-frequency stimulation to disrupt the local abnormal brainwave thereby blocking the patterns of activation that lead to symptoms of related diseases. Standard DBS does not adjust to varying conditions, such as short- or long-term changes in disease severity, including medication-related fluctuation.¹² The uniqueness of the Percept PC is in its ability for programming to identify the baseline brain state (without stimulation or medication), detect a specific brainwave (as a biomarker) associated with a patient's disease symptoms, and to adjust the DBS stimulation level based on the patient's symptoms. Thus, the neurologist can program a stimulation frequency range (therapeutic power band) that offers maximum symptomatic relief with minimal stimulation-induced side effects.^{1,5} The device is also able to sense and continually record the LFP at implanted DBS leads with or without stimulation.^{1,5} The enhanced abilities of the Percept PC are conferred by a proprietary technology called BrainSense technology.¹³

Compared with traditional DBS devices, the Percept PC stimulation is relatively insensitive to changes in the electrical properties (impedance) at the electrode-tissue interface, which have been reported to affect the quality of DBS readings.⁵

Who Might Benefit?

DBS is used to treat a wide variety of neurologic conditions.⁵ Because Percept PC allows the programming of different stimulation parameters for different symptoms, it can deliver stimulation in an individualized manner, offering the potential to achieve improved clinical efficacy with reduced side effects.⁵ Additionally, the ability to repeatedly record LFPs, both inside and outside of the clinic, provides clinicians and researchers with an unprecedented opportunity to advance understanding of the pathophysiology underlying neurologic and psychiatric disorders, such as major depression, obsessive-compulsive disorder, schizophrenia, Alzheimer disease, and addiction.¹⁴

Availability in Canada

Health Canada licensed the Medtronic PLC Percept PC DBS system with BrainSense technology for use in Canada in October 2020.¹³ It is authorized for therapy for neurologic disorders associated with Parkinson disease, essential tremor, dystonia, or epilepsy.¹³ Data on the uptake of Percept PC in Canada were not identified. However, a 2018 assessment

reported that the rate of DBS surgery was significantly higher than the national average in Saskatchewan (374%) and significantly below the national average in Quebec (40%) and Newfoundland and Labrador (32%).¹⁵ Since the study predates the introduction of Percept PC, its referenced DBS procedures must have been performed using the traditional devices without the BrainSense capability of Percept PC. The paper's authors found no significant difference between the percentage of people receiving DBS from rural areas and the percentage of the entire provincial population living in rural areas.

What Does It Cost?

There was no data identified on the specific cost of Percept PC to treat Parkinson disease or essential tremor in Canada. However, it has been reported that DBS is more cost-effective than drug therapy for advanced Parkinson disease.^{16,17} In the US, the cost of DBS implantation (i.e., surgery, devices, anesthesia, hospital fees, and physician fees) was estimated to be between \$70,000 and \$100,000 for bilateral procedures in 2018, whereas the cost of battery replacement varied from \$17,000 to \$27,000.¹⁸

Current Practice

Currently, the treatment is delivered continuously in people who require DBS therapy, and trained clinicians manually adjust the settings based on symptoms. Thus, patients may be exposed to unnecessary intensive energy, which may induce side effects.⁶

What Is the Evidence?

One prospective single-arm study¹⁹ based on clinical and neurophysiological data from 20 patients (14 with Parkinson disease, 5 with dystonia, and 1 with chronic pain) treated with Percept PC found that the device could record and monitor the most clinically relevant biomarkers for Parkinson disease and dystonia. Further, a case report⁷ on a 51-year-old man with Parkinson disease observed that Percept PC successfully recorded and adapted stimulations to beta oscillation fluctuations while the patient was outside the hospital without any stimulation-induced side effects.⁷

One descriptive review of the engineering underlying the development of the Percept PC device reported that the system's ability and functionality to chronically record LFPs at implanted DBS leads was validated in 14 patients with neurological disorders.⁵ The recordings were reported to proceed continuously in the presence of stimulation with in-built adjustment to prevent stimulation artifact from interrupting the measure of brain state.⁵

A prospective, single-blind, randomized crossover, multi-centre study in patients with Parkinson disease is under way to assess the adaptive DBS effectiveness of Percept PC. The estimated primary study completion is October 2022.²⁰

Safety

Side effects related to the therapy, device, or procedure can include (but are not limited to) intracranial hemorrhage, cerebral infarction, cerebrospinal fluid leak, pneumocephalus, seizures, surgical site complications, psychiatric and behavioural disorders, and device complications that may require surgical revision or removal of the implant.²¹

It has been reported that in October 2021, Medtronic issued an urgent field safety notice to health care providers in Europe that the Percept PC DBS implant may stop working and may need to be removed after a patient with an implant undergoes a cardioversion.²² If the device stops working, symptoms for which it was implanted are likely to return and may do so with greater intensity than before, resulting in a medical emergency in rare cases.²² The safety notice was issued to make health care providers and their patients aware of the possible risks of combining cardioversion and the Percept PC DBS implant, and weigh those risks against the benefits before implantation. The notice was also meant to inform patients already implanted with the Percept PC DBS device that it may need to be surgically replaced if they are due to undergo a cardioversion procedure.²² According to the report, Medtronic is in the process of adding information about the risks associated with cardioversion when using the Percept PC DBS device to its manual for prescribers.²²

Issues to Consider

The Percept PC system has not been compared with other such devices from an efficacy, efficiency, or cost-effectiveness standpoint. Also, there are no evidence-based recommendations for the use of individual devices in specific patient populations.^{2,19} It has been reported that critical aspects of concern related to the system, include background signal noise detection (artifact detection), data loss, and interference with or by other devices. Further, clinical effectiveness can be variable, with variation related to lead placement or a patient's unique physiology.⁴ Moreover, DBS programming is complex and time-intensive, even for experienced neurologists.⁴ Given these challenges and the inherent risks and adverse events of the DBS procedure, clinical expertise in selecting suitable patients is likely to be essential, and a step-by-step, multidisciplinary team approach may be necessary to carefully make the determination.¹⁸ DBS also commits patients to a lifelong implant, with subsequent battery replacements, which can be problematic in some patients, probably due to age and medical conditions.¹⁴ Further, the highly resource intensive nature and need for an expert multidisciplinary team to provide programs for patients and troubleshoot issues may restrict the use of Percept PC (and DBS in general) to large-volume resource-rich centres that may pose accessibility and equity concerns.^{14,18}

Related Developments

Because of its sensing capabilities, Percept PC can enable better understanding of disease-related brain activity patterns, their evolution over time, and their modulation in response to therapies.¹⁹ Thus, the device could allow the clinician to track patient-specific biomarkers over time and adjust treatment plans for improved patient outcomes in a variety

of conditions, while reducing the incidence of side effects due to imprecise stimulation.⁵ Apart from Parkinson disease, essential tremor, dystonia, and epilepsy, disorders currently under investigation with DBS include major depression, obsessive-compulsive disorder, tinnitus, Tourette syndrome, schizophrenia, Alzheimer disease, pain, addiction, and anorexia nervosa.¹⁴

A double-blind crossover study to evaluate the safety and efficacy of another adaptive DBS device in patients with Parkinson disease is currently ongoing, with an estimated primary completion date of November 30th, 2021.²³

Looking Ahead

As noted, many of the challenges related to DBS technology, such as side effects and variable clinical effectiveness, may be due to suboptimal placement of DBS leads.⁵ That may be explained by the fact that the location of the brain responsible for a particular disease symptom is small, making it challenging to place DBS leads in the correct area for optimal outcomes.⁵ It is expected that advances in neuroimaging and biological signals will enhance DBS lead placement precision.^{2,4} As studies in the field advance, increasingly sophisticated imaging techniques may be discovered to improve the identification and validation of appropriate brain targets, and confirm circuit engagements within these targets, likely helping to simplify programming, and reduce programming times.⁴ Possibilities also exist for new technologies that will allow closed-loop neuromodulation therapies, capable of adapting stimulation-based real-time symptom-specific and task-dependent input signals.¹⁹

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