Ontario Health Technology Assessment Series 2005; Vol. 5, No. 2

Deep Brain Stimulation for Parkinson's Disease and Other Movement Disorders

An Evidence-Based Analysis

March 2005

Medical Advisory Secretariat
Ministry of Health and Long-Term Care

Suggested Citation

This report should be cited as follows:

Medical Advisory Secretariat. Deep brain stimulation for Parkinson's Disease and other movement disorders: an evidence-based analysis. *Ontario Health Technology Assessment Series* 2005; 5(2)

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ISSN 1915-7398 (Online)
ISBN 978-1-4249-4320-3 (PDF)

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Abbreviations

ADL	Activities of daily living
ANAES	Agence Nationale d'Accréditation et d'Evaluation en Santé; National Agency for Accreditation and Evaluation in Health
CAPIT	Core Assessment Program for Intracerebral Transplantation
CI	Confidence interval
DBS	Deep brain stimulation
ET	Essential Tremor
GP	Globus pallidus – internal segment
L-dopa	Levodopa
LID	Levodopa-induced dyskinesia
MSAC	Medical Services Advisory Committee
NICE	National Institute of Clinical Excellence
PD	Parkinson's disease
QALY	Quality adjusted life year
RCT	Randomized controlled trial
SD	Standard deviation
STN	Subthalamic nucleus
TH	Thalamus

Scales

UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS II	Unified Parkinson's Disease Rating Scale, Activities in Daily Living
UPDRS III	Unified Parkinson's Disease Rating Scale, Motor Function
UPDRS IV	Unified Parkinson's Disease Rating Scale, Motor Complications and Reduction in Dose

Executive Summary

Objective

To determine the effectiveness and adverse effects of deep brain stimulation (DBS) in the treatment of symptoms of idiopathic Parkinson's disease, essential tremor, and primary dystonia and to do an economic analysis if evidence for effectiveness is established.

The Technology

Deep brain stimulation (DBS) is a surgical procedure indicated in the relief of motor function symptoms of Parkinson's disease, essential tremor and dystonia. It involves the surgical implantation of the DBS device, which include the implantable pulse generator or stimulator, the extension, and the lead. The electric impulse is produced within the stimulator component, and transmitted to the brain site by the extension and the lead(s). DBS surgery can be either unilateral or bilateral. The laterality of the surgery and target area for brain stimulation may vary with the type of symptom or spectrum of symptoms, and such decisions are made on a case-by-case basis.

Advantages of DBS over ablative surgery is that it is comparatively less invasive, it is reversible, and it allows for stimulation of both sides of the brain. Ablative surgery, which is not practiced in Ontario, results in a non-reversible lesion and is often not conducted on both sides. Thus far, DBS has been considered as an adjunct to drug therapy.

Review Strategy

The standard Medical Advisory Secretariat search strategy was conducted to identify international health technology assessments and English language journal articles published from January 1, 2001 onwards. Documents were reviewed separately for Parkinson's disease, essential tremor and primary dystonia.

Summary of Findings

There is level 1b evidence that bilateral DBS of the subthalamic nucleus is effective in the short-term control of advanced parkinsonian symptoms, and there is level 3a evidence that the effect is sustained for at least 5 years.
There is Level 3a evidence that DBS of the thalamus is effective in the control of tremor in patients with essential tremor and PD for at least 6 years.
There is level 3a evidence that bilateral DBS of the globus pallidus is effective in the control of symptoms of primary dystonia for at least 1 year.

Conclusion

- According to the estimates of prevalence and evidence of effectiveness, there is a shortfall in the numbers of DBS currently done in Ontario for drug-resistant PD, essential tremor, and primary dystonia.
- Since complication rates are lower if DBS is performed in specialized centres, the number of sites should be limited.
- The cost per procedure to institutions with the expertise to undertake DBS and the human resource

considerations are likely to be limiting factors in the further diffusion of DBS.

Objective

To conduct a systematic review of the evidence on the effectiveness of deep brain stimulation (DBS) in the control of symptoms of Parkinson's disease (PD) and other movement disorders in patients that are refractory to treatment. This review also has information on complications related to DBS as reported in the studies of effectiveness included in this review, and an economic analysis.

Background

Clinical Need: Target Population and Condition

DBS is a surgical option for patients with movement disorders that are no longer adequately controlled by drug therapy (i.e., those who are refractory to treatment). These movement disorders include conditions such as PD, essential tremor, and primary dystonia, each of which is discussed in this review. Other rare disorders may also be occasionally considered for this therapy. Refractory to treatment is defined as either suboptimal response to treatment; or motor fluctuations that may arise from disease progression, or complications of drug therapy, or both. The diseases discussed here are similar in that they are all neurodegenerative conditions, but they differ in their clinical presentation and may vary in the laterality of their symptoms.

Parkinson's Disease

The etiology of PD is not known, although neuropathologic findings suggest progressive cell death primarily in the substantia nigra pars compacta, the origin of the nigrostriatal tract in the brain. The pars compacta contains about 450,000 neurons that produce dopamine (dopaminergic neurons). Degeneration of these neurons, called neurodegeneration, may be a result of oxidative stress, programmed cell death (apoptosis), and/or detrimental changes in mitochondrial DNA, although these causative factors have not been universally accepted. (1;2) Neuron changes in these regions result in dopaminergic deficiency, which is one of the targeted pathways for medical treatment, hence the administering of levodopa (or L-dopa).

Epidemiologic hypotheses have focused on the interaction of environmental and genetic factors, although a specific environmental exposure factor has yet to be identified. The main risk factor for PD is increasing age, with only 5% to 10% of patients having disease onset before the age of 40. Family history is also an important risk factor. (1;2)

The natural history of PD is not clearly defined, yet symptoms may appear as unilateral (on one side of the body) in early disease. Disease progression likely involves the expansion of symptoms resulting in what is essentially a bilateral condition. For these reasons, the majority of DBS surgeries for PD are bilateral. The distribution of the age at onset for PD varies with the type of motor symptoms as follows:

- In tremor-predominant PD, the age at onset is monophasic with a peak at about 60 years.
- In akinetic-rigid PD, the age-of-onset is biphasic. Early-onset disease peaks in the middle of the sixth decade, and late-onset dystonia in the first half of the seventh decade.
- The risk of mixed type (tremor and akinetic-rigid) PD increases with age. (3)

The average duration of PD in studies of DBS included in this review ranged from 10 to 15 years.

Diagnosis of Parkinson's Disease

The gold standard for diagnosis of PD is the neuropathological examination. Since there are no known clinical biomarkers for disease detection, diagnosis is based on clinical criteria. The 3 main features of this condition are tremor, rigidity, and motor dysfunction such as freezing and bradykinesia (slowness of movement). In the early stages of PD, symptoms and signs are asymmetrical. With disease progression, however, PD becomes a bilateral condition. (1;2;4) Clinical presentation of PD may include slowness in activities of daily living (ADL) such as dressing, walking, and doing household chores; difficulty and taking longer to get up from a chair; reduced arm swing; flexed posture and a shuffling gait (bradykinesia); rigidity; and cogwheeling (ratchet-like feel of muscles) on passive movement.

The clinical examination should exclude parkinsonism due to other conditions, since parkinsonian symptoms can be present in conditions other than Parkinson's disease. The differential diagnosis of PD includes progressive supranuclear palsy, multiple system atrophy, vascular parkinsonism, diffuse Lewy body disease, and corticobasal degeneration. (5)

Responsiveness to L-dopa has been used to distinguish between PD and other atypical parkinsonism, though its utility as a diagnostic tool is not widely accepted. The clinical examination should include evaluation of vertical eye movement to rule out progressive supranuclear palsy; postural blood pressure changes, other autonomic abnormalities, and cerebellar features to rule out multiple system atrophy. Early dementia and other features may suggest Lewy body dementia, corticobasal degeneration, or vascular parkinsonism. Patients with early-onset parkinsonism should assessed for Wilson's disease. (5;6)

Medical Treatment

Treatments for PD aim to improve motor function and quality of life. Clinical management varies with disease severity and the age of the patient. The severity of disease is defined as the degree of functional disability, whereas the age of the patient is important with respect to the adverse effects of the drug being prescribed. (5)

For patients with mild to moderate functional impairment, pharmacotherapy includes giving a dopamine agonist, then adding L-dopa when symptoms are no longer well controlled. (6) The dose of L-dopa is gradually increased with symptom progression, and a catechol O-methyltransferase inhibitor may be added to improve the pharmacokinetics of L-dopa to extend its half-life. With prolonged use, however, clinical symptoms may reflect the combined effects of the disease, and the benefits and adverse effects of L-dopa. These combinations can result in motor complications such as on-off fluctuations and levodopa-induced dyskinesias (LIDs). On-off fluctuations, also referred to as the on-off phenomenon, are characterized by rapid alternation between the "on" state (good motor function) and the "off" state (poor motor function). Whereas this phenomenon is unrelated to the timing of the dose, levodopa-induced dyskinesias are involuntary movements due to the build-up of the drug.

The likelihood of L-dopa-induced motor complications increases with longer use and higher dosages. The rate of becoming refractory to treatment has been estimated at about 10% with each year of use. (7) The types of complications may include motor fluctuations, wearing-off effects of the drug, and/or dyskinesias. The range of prevalence estimates of these complications, derived from individual studies are as follows: from 10% to 59% for fluctuations; from 20% to 52% for wearing off of the L-dopa effect before the next dose; and from 20% to 56% for dyskinesias. (6) The length of follow-up in these studies ranged from 2 to 6 years.

Standard care for patients with advanced PD includes modifications in their drug regimen, and the possible introduction of drug holidays. Drug holidays are phases in which drug therapy is eliminated and then reintroduced at possibly lowered doses. For patients with motor fluctuations that are not adequately controlled by drug therapy, surgical intervention in the form of DBS may be an option. Nevertheless, evaluation of patient eligibility for DBS surgery must follow specific guidelines and is best done within a multidisciplinary expert centre. Expert consultation indicates that about 10% to 15% of all patients with PD become candidates for DBS. (Personal communication with clinical expert, February 2005)

Patient Selection Criteria for Deep Brain Stimulation

The evolving evidence on the risks and benefits of DBS warrants the careful selection of patients for this procedure. Such selection is intended to ensure the identification of patients most likely to benefit from DBS in the presence of significant risks associated with the procedure.

The main criterion to determine if a PD patient with PD is eligible for DBS is sensitivity to L-dopa. Responsiveness to an L-dopa challenge test has been found to be a strong predictor of DBS outcome; thus, it remains the main criterion of eligibility for this surgery. The procedure for the L-dopa challenge and measures of responsiveness are outlined in a diagnostic and methods core evaluation tool called the CAPIT protocol (Core Assessment Program for Intracerebral Transplantation). (8) This protocol was developed as a minimum methodological standard to enable common practices between centres in the selection of and evaluation of patients for, in this case, DBS.

The CAPIT protocol has 2 main sections. The first is a description of the L-dopa challenge to be followed in assessing responsiveness to the drug. The test procedure includes a 12-hour drug-washout period (overnight withdrawal of drugs) before the patient is tested in the morning, but not within 1 hour of waking (to eliminate sleep benefit), first without medication (meds-off condition) and then 1 to 2 hours after L-dopa intake (meds-on condition) at the regular daily dose. Unequivocal responsiveness to L-dopa is defined as a 33% or greater improvement in at least 1 of these 4 clinical motor function tests:

- Pronation-supination test
- Hand/arm movement between 2 points
- Finger dexterity
- Stand-walk-sit test

If responsiveness is not achieved, testing is repeated in 1 week at 1.5 times the dose, and again in 1 week for a final challenge at 2 times the dose, after which the patient is considered ineligible for DBS. If the patient is responsive to L-dopa, additional criteria to be considered are the absence of substantial medical problems, major cognitive impairment, and psychiatric illness; and the presence of motor dysfunction as measured by the Unified Parkinson's Disease Rating Scale (UPDRS). Other contraindications are exposure to diathermy and magnetic resonance imaging using full body radio frequency coil or head transmit coil; patients for whom the test stimulation (test conducted before full implantation the day of the DBS surgery) was unsuccessful; those unable to operate the device control; and those with a cardiac pacemaker.

The second portion of the CAPIT protocol has a description of outcome measures to be included in the assessment that are based on the UPDRS scale (version 3.0), a measure of overall motor function. The UPDRS is a questionnaire that includes sections on motor function, ADL, and percentage of the waking day spent in good/poor function. This scale has been used throughout the different studies in this review to measure outcomes. Other outcome measures in this review are drug dose reduction, an important

factor in the assessment of the effectiveness of DBS, which is captured either in daily diary reports or during clinic visits; and the percent of the waking day spent in poor function derived from either question 39 of the UPDRS scale or from daily diaries. The maximum total score for the UPDRS is 199. The UPDRS sections specific to this review are outlined in Table 1.

Table 1: Unified Parkinson's Disease Rating Scale and Outcome Measures

Outcome Measure (Data Source)	UPDRS* Item(s) Number	Range of Scores	Definition of Improvement of Function
Motor function (UPDRS III)	18–31	0–108	Decrease in score
Activities of daily living (UPDRS II)	5–17	0–52	Decrease in score
% waking day in poor function ("off state")	39; daily diaries	0–4; % of day	Decrease in score Decrease in % of day

*UPDRS indicates Unified Parkinson's Disease Rating Scale.

An important distinction among these 3 subscales is the 'time frame' of the function being captured. For example, the motor function assessment pertains to function at the clinic visit and thus captures information for this time only. Questions on ADL, however, pertain to function over a longer period: the patient is asked to report on assistance required with, for example, dressing, hygiene, turning in bed, and the frequency of events such as falling and freezing when walking. The measure that best captures motor function throughout the day comes from daily diary data, in which the patient reports the amount of time spent in good function with dyskinesia, good function without dyskinesia, or poor function at 30-minute intervals. The improvement in the percent of the waking day spent in good function without dyskinesia after surgical implantation of the DBS stimulator on (DBS on) compared with the baseline preimplantation state (without DBS), indicates how well DBS assists in stabilizing good function throughout the day. The lack of functional stability has been previously described as the on-off phenomenon, in which maximal benefits of the drug are not maintained throughout the day.

Essential Tremor

Essential tremor is the most common adult tremor disorder. Tremor is typically evident on both sides of the body. Tremor occurs during voluntary movement, which is distinguished from tremor-predominant PD with symptoms occurring only at rest. Furthermore, disease progression in essential tremor typically results in an increase in intensity of symptoms without a corresponding expansion of symptoms, in contrast to the expansion of symptoms in PD. This differential pattern in disease progression between the 2 diseases is the main reason for the implantation of a unilateral DBS device in essential tremor and a bilateral device in PD (i.e., it may be sufficient to reduce the tremor on the dominant arm in essential tremor, however, bilateral surgery may be necessary in some patients). The main neuronal site for stimulation in essential tremor is the thalamus.

Essential tremor is familial in 50% to 70% of patients (hereditary and sporadic forms), with hereditary forms attributable to an autosomal dominant pattern of inheritance with variable penetrance. About 50% of patients have an affected first-degree relative (parent or child). (9) The age of onset of essential tremor is bimodal: early onset occurs before the age of 20, and late onset occurs most often in the sixth decade of life.

The degree of severity varies among patients, and only 50 to 60% of people who have more severe

symptoms seek medical care; of those that seek medical care, 50% have symptoms severe enough to require drug therapy. (Personal communication with clinical expert, February 2005) The clinical management of essential tremor with medications includes β-adrenergic antagonists (e.g., propranolol and sotalol), anticonvulsants (primidone, topiramate), benzodiazepines (alprazolam), and neuroleptics (clozapine). Propranolol and primidone are prescribed in early disease, although loss of efficacy after 1 year of use results in dosage increases. (9)

Expert opinion suggests that about 60% of patients on drug therapy have suboptimal response and/or adverse effects, with 5% to 10% becoming eligible for DBS. (Personal communication with clinical expert, February 2005) Unlike PD patients with refractory disease, patients with essential tremor may stop drug therapy entirely if the medications are not working.

Primary Dystonia

Dystonia is considered a syndrome of different causes, and not a specific disease entity. The symptoms that characterize this syndrome are muscle contractions with twisting and odd posture. Primary dystonia, that which is idiopathic or genetically determined, is the most common form. The age of onset of this condition is earlier than in PD, with the DYT1 gene causing a large proportion of early-onset dystonia. (10) Early-onset dystonia (< 20 years) occurs most often in a limb and has a tendency to generalize to other body parts with disease progression, whereas late-onset disease (> 20 years) occurs most often in focal or segmental forms. Therefore, either unilateral or bilateral DBS may be performed, depending on the laterality of symptoms.

The primary target for neurosurgery in the mid-1970s was the thalamus, but with improvement of dystonic symptoms in PD following pallidotomy, the globus pallidus has become the brain site of interest for such symptoms.

Epidemiology of Parkinson's Disease, Essential Tremor, and Primary Dystonia

Parkinson's Disease

A cross-sectional study of the Ontario Health Insurance Plan and Ontario Drugs Branch, Ministry of Health databases from 1992 to 1998 revealed an average annual crude prevalence rate (per 1,000 population 25 years of age or older) of 3.59 for males and 3.21 for females. These rates varied by age. The highest was among those 60 years of age or older. Among women, the rate for the older group was 11.21 per 1,000 population, compared with 0.30 for those aged 25 to 59 years. A similar pattern was observed for males, with the rate being 14.63 and 0.41 per 1,000 population for the older and younger groups, respectively. More than 90% of patients were older than 60 years. (11)

The prevalence of PD in the general population has been estimated at 0.3%. Risk of PD, however, increases exponentially from age 65 onwards, for an estimated prevalence of 3.0%. (1;2) If the overall population estimate of 0.3% were applied to an approximate Ontario population of 12.3 million people, the estimated number of people with PD in this province would be 37,000. This number is consistent with that of the Parkinson Society Canada, (12) (which estimates there are 100,000 patients with PD in Canada; given that Ontario has 38% of the country's population, the expected number of people with PD in Ontario is 38,000.

Expert opinion indicates that the percentage of patients eligible for DBS may be as high as 10% to 15%, for a total of 3,700 to 5,550 prevalent cases in the province (based on 37,000 PD patients). (Personal communication with clinical expert, February 2005) More conservative estimates, which are based on the proportion of patients likely to consent to surgery, are in the range of 5%, resulting in an estimation of

about 1,850 people. (Personal communication with clinical expert, February 2005)

Essential Tremor

The prevalence of essential tremor in the general population is 0.3%. In those aged 65 years or older, it is 14.0%. (9) This translates into an estimated prevalence in Ontario of 37,000 people with essential tremor, of which 50% (18,500) to 60% (20,500) will seek medical care. Of those diagnosed, 50% will have symptoms severe enough to be treated with drug therapy (range, 9,250 to 10,250), and 60% of these (range, 5,550 to 6,150) will have a suboptimal response and/or adverse effects. A maximum of 5% of these patients may be eligible for and consent to DBS, thus resulting in a final number of 308.

Primary Dystonia

Prevalence estimates for this condition vary highly from one country to another, with the lowest rates observed in Japan and the highest rates in the United States. (10) On the basis of a record-linkage study (13) conducted for 1952 to 1980 in the United States for all ages combined, the prevalence of early-onset dystonia was estimated to be 34 (95% CI, 2–124) per million. For late-onset dystonia, it was estimated to be 295 (95% CI, 172–479) per million. In a more recent study, Risch et al. (14) found prevalence estimates for early-onset dystonia (defined as younger than 28 years) were generally higher in Ashkenazi Jews in the United States, at 50 (95% CI, 39-63) per million.

Prevalence estimates used in this report are applicable to the general population. Based on a provincial estimate of 3 million people (2004 estimates (15) aged less than 20 years (2.2 million people aged 0 to 14 years, and 0.8 million people aged 15 to 19, based on a rate of 2.2 million per 14 years of age per year), and a rate of 34 per million, the expected number of prevalent cases of early-onset primary dystonia in Ontario is 102. The number of prevalent cases of late-onset dystonia (based on a population estimate of 12 million minus 3 million) in people 20 yearsq of age or older is 2,655. Therefore, the total number of people with primary dystonia in Ontario is about 2,757. Of patients with early-onset dystonia, and assuming that 75% of patients are eligible for DBS, the number of eligible patients would be 75. For late-onset dystonia, assuming a proportion of 10% eligible, the number of patients would be 265. Therefore, the total number of patients with primary dystonia that might be eligible for DBS is about 340.

Existing Treatments Other Than Technology Being Reviewed

For all stages of PD, drug therapy is the medical treatment of choice. Although different drugs and dosages can be prescribed at the different stages of disease severity, as previously described, L-dopa is the gold standard to manage dopamine-related motor dysfunction in PD. (7) Nevertheless, as the degree of striatal denervation increases in disease progression, with subsequent increases in drug dose, the rate of developing motor complications is about 10% per year. This figure suggests, for example, that after 7 years, 70% of PD patients on L-dopa will have had treatment-related motor fluctuations. Due to restricted eligibility criteria, 10% to 15% of these patients are eligible for surgical intervention.

Inadequate pharmacologic control of motor fluctuations in other movement disorders, like essential tremor and primary dystonia, suggest that surgical intervention might also be an option for people with these conditions.

Presently, the 2 options for surgical intervention are ablative surgery and DBS, but the former is not done in Ontario. It is irreversible and associated with considerable risks. (Personal communication with clinical expert, February 2005) Furthermore, often lesions are conducted unilaterally since the introduction of DBS, because the brain cannot sustain lesions on both sides. Thus, in cases of bilateral disease, ablative surgery may not be as helpful for ipsilateral symptoms (symptoms on same side of the

body as the side of the lesion). In PD, for example, neuroablative surgery may be useful in the early stages of the disease where only one side is affected, but it is not indicated in people with bilateral disease. At present, the only surgical option done in Ontario for patients with advanced movement disorders refractory to drug treatment is DBS.

New Technology Being Reviewed: Deep Brain Stimulation

The History and Development of Deep Brain Stimulation

Interest in surgical intervention for the control of parkinsonian symptoms waned with the availability of L-dopa in the late 1960s. Ablative surgeries were largely abandoned due to the high risks and their invasiveness. With the emergence of data on the long-term effectiveness, or rather ineffectiveness, of L-dopa in the control of parkinsonian symptoms over time, interest in surgical interventions re-emerged, particularly for this subgroup of patients. DBS is the preferred surgical procedure because it is reversible and can accommodate bilateral stimulation of the brain.

Neurologists and neurosurgeons first used electrical stimulation of the brain in the 1960s to locate specific surgical sites of the brain. During these procedures, the discovery of the suppression of neurologic symptoms of essential tremor and PD led to the development of DBS devices in the 1980s. In 1987, Bernabid and Pollak at the University of Grenoble, France, implanted the first stimulation device for disabling tremor, and in August 1992, the first European multicentre study of more than 100 tremor patients began. In 1995, Medtronic's DBS device for thalamic stimulation in the relief of essential tremor and tremor in PD was made commercially available in Europe, Canada, and Australia. Medtronic Inc. is the only manufacturer and distributor of DBS devices in Canada.

Description of the Device

The DBS system is a pacemaker-like device with 3 implantable components:

- A neurostimulator (includes battery pack and electric impulse generation components)
- An extension (connects neurostimulator to leads)
- A lead (thin coiled wire contained in polyurethane insulation)

Either a unilateral or a bilateral device may be implanted, with 1 and 2 leads, respectively. The lead is inserted into the brain through small holes in the skull (burr-hole approach) while the patient is awake, to ensure the accuracy of the brain site. The extension is then passed subcutaneously over the skull to the shoulder area to connect to the neurostimulator. The neurostimulator is inserted near the clavicle or the abdomen under general anesthesia. The surgery takes all day and requires hospitalization for a few days.

Rationale Behind its Use

Thus far, DBS has been considered an adjunct to drug therapy. While the mechanism of action for DBS is not known, its effect on the patient may result in the stabilization of motor function throughout the day. As described, on-off fluctuations refer to the extremes of maximal benefit of the drug (on-state) and minimal benefit of the drug (off-state). DBS is thought to be most effective in the off state, when the relief of symptoms from drugs is minimal and thus helps to stabilize symptoms throughout the day.

The brain region most suitable for stimulation has not yet been standardized. The location may vary with the symptom profile of the patient. In general, however, the target areas for DBS stimulation are as follows, with the accompanying symptom:

- Thalamic region – predominantly for tremor
- Subthalamic region – for tremor, dyskinesia, rigidity, bradykinesia, akinesia, speech difficulties, and freezing
- Globus pallidus, internal segment region – for dyskinesia, tremor, rigidity, bradykinesia, and akinesia

In general, the site of stimulation for parkinsonian symptoms is the subthalamic nucleus or internal segment of the globus pallidus. For symptoms of tremor, whether for essential tremor or tremor-predominant Parkinson's disease, the site of interest is primarily the thalamus, and for primary dystonia it is the internal segment of the globus pallidus. Much more often, however, other targets are more appropriate (even for isolated parkinsonian tremor). (Personal communication with clinical expert, February 2005) Such decisions are made on a case-by-case basis.

Associated Benefits and Risks

Impact on Daily Living

Reported benefits of DBS include improved motor function in patients who have symptoms that drugs do not control adequately. In some cases, particularly in PD, a person experiences a transition from a lifestyle completely dependent on a caregiver to one of relative independence. The daily experience for the person with PD after DBS may include less akinesia and other motor dysfunction (for which an ambulance may have to called). Thus, DBS has the potential to reduce the enormous personal and social costs associated with these neurodegenerative conditions.

An additional benefit of DBS is its ability to reduce daily drug intake in some people. The average daily reduction in L-dopa intake in PD is about 50%, and a smaller proportion of people stop taking drugs completely. In patients who have bilateral DBS for essential tremor, most stop taking drugs after the surgery; however, patients who have unilateral surgery who have motor dysfunction on the ipsilateral side (the other side than that affected by the unilateral implant) are likely to continue with drug therapy.

Data on risks associated with DBS have been extracted from the studies reviewed and are discussed in a section below.

Regulatory Status

Medtronic Inc. (Minneapolis, MN) is the only company that manufactures and distributes DBS devices in Canada. Health Canada has approved 2 models, 1 for the control of symptoms of Parkinson's and the other for tremor. The first device, the Kinetra Neurostimulator System (Licence 372) can accommodate unilateral and bilateral brain stimulation to relieve parkinsonian symptoms. The Soletra Neurostimulator System (Licence 25235) is approved for unilateral stimulation and is indicated in the relief of tremor associated with Parkinson's and essential tremor. The labeling of this device is presently under review, and if approved, will be indicated in dystonia, too. Both neurostimulation systems are approved as Class IV devices.

DBS is indicated for patients with advanced disease and significant functional disability that is refractory to drug therapy. They must also be able to properly operate the stimulator. In the case of Parkinson's disease, the patient must also be responsive to L-dopa. Contra-indications include exposure to magnetic

resonance imaging (MRI) and exposure to diathermy. Safety precautions must be followed.

Literature Review on Effectiveness

Objective

- To determine the effectiveness and adverse effects of DBS in the treatment of symptoms of idiopathic Parkinson's disease, essential tremor, and primary dystonia and to do an economic analysis if evidence for effectiveness is established.

Questions Asked

- In people with Parkinson's who have become refractory to L-dopa, does bilateral DBS of the subthalamic nucleus improve motor function, ADL, and/or reduce the adverse effects of L-dopa by permitting a lower dose of L-dopa to be used?
- In patients with essential tremor, does unilateral or bilateral DBS of the thalamus improve their symptoms?
- For patients with primary dystonia, does unilateral or bilateral stimulation of the globus pallidus improve symptoms?
- What are the adverse effects of DBS?
- What are the economic considerations if evidence for effectiveness can be established?

Methods

Electronic databases searched were Ovid MEDLINE, EMBASE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and INAHTA.

Keywords: Electric stimulation or electric stimulation therapy; electrodes, implanted; deep brain stimulation; neurostimulation; thalamic, subthalamic, pallidal; Activa or Kinetra or Soletra; Parkinsonian Disorders; Dyskinesias; Dystonia; Essential Tremor; Dystonic Disorders; Multiple Sclerosis.

Time frame: The most recent studies included in the health technology assessments of PD were from 2001; therefore, the start date for inclusion of studies in this assessment was January 1, 2001.

Excluded were case reports, comments, editorials, and letters. More than 1,000 articles, including previously published health technology assessments, were identified. When the search was restricted to Parkinson's disease, essential tremor, or dystonia, and searched manually for published articles on RCTs or clinical studies, it yielded 338 citations. These were examined against the criteria, as described below, and resulted in the inclusion of 5 health technology assessments and 12 articles on PD, 4 on essential tremor, and 1 on primary dystonia.

Inclusion Criteria

- English-language articles and health technology assessments from January 1, 2001 onward
- Conditions of idiopathic PD, essential tremor, and primary dystonia, with a focus on the outcome of motor function.
- Studies of PD that focus on bilateral DBS of the subthalamic nucleus only
- Minimum sample size of level 1 or level 2 evidence, n = 10; of level 3 evidence, n = 25 for PD and

essential tremor, and n = 10 for primary dystonia.

- Minimum follow-up for level 3a evidence (only for studies that do not have a randomization component) of 12 months.

Exclusion Criteria

- Studies without contemporaneous controls
- Studies that do not assess motor function (e.g., studies on technical aspects, cognitive function, gait, and posture)
- Studies with sample sizes less than 10 or 25 (as outlined above) for the question being addressed
- Studies that compare the effectiveness of stimulation in different locations of the brain
- Studies that compare DBS with other surgeries
- Studies in which patients are not surgically naïve, i.e., exclusion of studies in which patients have had ablative surgery prior to DBS.

Intervention

- Bilateral DBS for parkinsonian symptoms, and unilateral or bilateral stimulation to suppress the symptoms of essential tremor or primary dystonia.

Comparators

- Studies in which there was a comparison group of either diseased or healthy subjects or one in which subjects served as their own control were included.

Outcomes of Interest

The values at follow-up (i.e., after implantation) compared with baseline values (i.e., before implantation) for the following outcome measures:

- Motor function, including tremor
- ADL
- Percent of the day spent with motor dysfunction
- L-dopa equivalent daily dosage

Results of Literature Review

The authors and foci of the 4 health technology assessments of DBS in PD are shown in Table 2. An additional assessment was found for DBS in movement disorders other than PD, and is presented after the discussion for PD.

Table 2: Summary and Focus of Previous Health Technology Assessments on Parkinson's Disease

Year	Author, Country	Focus of Assessment
2003	National Institute of Clinical Excellence, United Kingdom	Safety and efficacy of DBS-STN* in patients with PD*
2002	l'Agence Nationale d'Accréditation et d'Evaluation en Santé, France	Safety and efficacy of DBS in PD patients refractory to medical therapy but remain sensitive to L-dopa
2002	Blue Cross and Blue Shield, United States	Improved health outcomes associated with bilateral DBS of the STN or globus pallidus in advanced PD
2001	Medical Services Advisory Committee, Australia	Effectiveness of DBS relative to ablative surgeries; effectiveness of DBS on its own

*DBS indicates deep brain stimulation; PD, Parkinson's disease; STN, subthalamic nucleus.

Summary of Findings on Effectiveness

The findings and conclusions on the effectiveness of DBS from the 4 health technology assessments are summarized below, followed by the Medical Advisory Secretariat's literature review. The final portion of this section includes one health technology assessment on essential tremor and dystonia. This is followed by a literature review on each of these conditions.

National Institute of Clinical Excellence (NICE), United Kingdom (16)

Deep Brain Stimulation for Parkinson's Disease

Objective: To determine the safety and efficacy of stimulation of the subthalamic nucleus in patients with PD who have become refractory to medical treatment

Comments: Laterality (unilateral or bilateral) of surgery not specified.

Studies Included	Findings	Conclusions
➢ 2 systematic reviews ➢ 1 RCT* ➢ 6 non-RCTs ➢ 8 case series with at least 50 subjects ➢ 9 small comparison studies	➢ Improved motor skills, function, and movement in patients with PD*	➢ Safety and effectiveness data adequate to support DBS in patients with PD who have become refractory to standard medical treatment, providing for consent, audit, and clinical governance ➢ Patient selection by multidisciplinary team. ➢ Results of PDSurg trial to be reviewed when available.

*PD indicates Parkinson's disease; RCT, randomized controlled trial.

L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES), France (17)

Evaluation of Deep Brain Stimulation in Idiopathic Parkinson's Disease

Objective: To determine the safety and efficacy of DBS in Parkinson's disease
Subjects: Patients with PD that no longer respond to medical treatment, but who must have retained good sensitivity to L-dopa
Comments: Laterality (unilateral or bilateral) of surgery not specified. DBS stimulation site not restricted.

Studies Included	Findings	Conclusions
➢ 3 RCTs ➢ 2 non-RCTs ➢ 3 summary reviews ➢ 5 case series	➢ Lack of good RCTs hampers efficacy and safety assessment ➢ Stimulation of STN or GP seems effective in short-term for PD. ➢ Thalamic DBS* effective for tremor	➢ DBS is feasible; however, benefit-risk ratio not adequate for indications proposed ➢ Recommend involvement of expert centres for further assessment

*DBS indicates deep brain stimulation; GP, globus pallidus; PD, Parkinson's disease; RCT, randomized controlled trial; STN, subthalamic nucleus.

Blue Cross and Blue Shield, United States (18)

Bilateral Deep Brain Stimulation (DBS) of the Subthalamic Nucleus (STN) or the Globus Pallidus Interna (Gpi) for the Treatment of Advanced Parkinson's Disease

Objective: To determine whether bilateral DBS of the subthalamic nucleus or globus pallidus improves health outcomes in PD
Subjects: Patients with medically refractory PD (e.g., with "on-off" fluctuations, severe immobility, and/or L-dopa induced dyskinesias)
Comments: Bilateral surgery only.

Studies Included	Findings	Conclusions
DBS* of the STN:* ➢ 1 RCT* ➢ 12 single-centre studies of < 25 patients ➢ 1 large case series DBS of the GP:* ➢ 2 RCTs ➢ 7 non-RCTs	➢ In 1997, found effectiveness of unilateral DBS of the thalamus for patients with disabling, medically unresponsive tremor, due to essential tremor or PD.* ➢ For bilateral DBS of STN or GP, there are no large long-term RCTs, but the published evidence is compelling due to numbers, consistency in findings, and magnitude of clinical improvement.	➢ DBS of the STN relieves motor fluctuations, "off" state immobility and "on" state dyskinesias in PD. ➢ Magnitude of change in motor function and reproducibility of results demonstrate effectiveness of DBS of the GP.

*DBS indicates deep brain stimulation; GP, globus pallidus; PD, Parkinson's disease; RCT, randomized controlled trial; STN, subthalamic nucleus.

Medical Services Advisory Committee (MSAC), Australia (19)

Deep Brain Stimulation for the Symptoms of Parkinson's Disease

Objective: To determine the effectiveness and safety of DBS relative to other surgeries, and on its own, in the control of parkinsonian symptoms
Subjects: Patients with PD for whom medical therapy no longer provides a smooth or sustained motor response
Comments: DBS of the subthalamic nucleus, globus pallidus, or thalamus.

Studies Included	Findings	Conclusions
➢ DBS-TH* and thalamotomy: 1 RCT;* ➢ DBS-GP* and pallidotomy: 1 RCT; ➢ DBS-STN* and ablative surgery: no studies. ➢ DBS compared to medical treatment: 2 health technology assessments	➢ DBS-TH relative to thalamotomy: At 6 mos: DBS significantly improved some aspects of quality of life. ➢ DBS-GP relative to pallidotomy: At 3 mos: no significant difference between them. ➢ DBS-STN relative to ablative surgery: no studies found. ➢ DBS relative to medical treatment: Could not be determined owing to methodological limitations.	➢ To prove DBS is more effective than surgery, more rigorous study required ➢ DBS compared with medical therapy: RCTs assessing long-term effectiveness required, accounting for quality of life and Parkinson's symptoms ➢ Recommend interim funding provided subject participation in an RCT, limited to centres with appropriate expertise

*DBS indicates deep brain stimulation; RCT, randomized controlled trial; STN, subthalamic nucleus; GP, globus pallidus; TH, thalamus.

It is important to note that generally, the health technology assessments analyzed the same studies, in particular, the same RCTs. Effectiveness of DBS in PD was evident in 3 of the 4 assessments, although the laterality of effect and location of stimulation was not examined consistently across all of them.

The most recent and specific review was conducted by the National Institute of Clinical Excellence (NICE) and focused on the effectiveness of bilateral DBS of the subthalamic nucleus. Conclusions are supportive of the careful selection of patients likely to benefit from DBS and recommendations for implementation include clinical audit and informed consent, owing to risks associated with the procedure.

Blue Cross and Blue Shield in the United States determined that the evidence in support of the effectiveness of DBS was sufficient. The review by the Australian Medical Services Advisory Committee (MSAC) recommended interim funding, provided subjects participate in a long-term RCT. The MSAC recommendation was based on the conclusion that the effectiveness of bilateral DBS of the subthalamic nucleus and globus pallidus was unclear relative to ablative surgery or medical therapy.

L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) concluded that the risk-benefit ratio for DBS was not adequate, and recommended further assessment by expert centres.

Examination of these health technology assessments suggests that research in the field of neurostimulation is developing rapidly. Although the initial assessments were non-specific on the questions being examined, the focus of more recent assessments reflects advances in knowledge in recent years. In these reviewed assessments, the main outcomes of interest were motor function and safety. However, the percent of the waking day spent with good function and reduction in L-dopa dose, now regarded as important outcomes, were not necessarily commented on.

A summary of the data on adverse events, as reported in the 4 assessments reviewed, is shown in Table 3. Transient and permanent risks have been reported. The review by NICE reported on the risk of stroke.

Table 3: Adverse Events as Summarized in Health Technology Assessments for Deep Brain Stimulation in Parkinson's Disease

Year	Author	Adverse Events
2003	National Institute of Clinical Excellence, United Kingdom	Complications include risk of stroke, confusion, speech disorders, and vision problems. Risk of stroke found to be 3%.
2002	L'Agence Nationale d'Accréditation et d'Evaluation en Santé, France	Did not report data, but indicated the paucity of medical device vigilance reports suggest under-reporting of adverse events. Three main types of adverse events related to: surgery (hemorrhage), the medical device (infection, dysfunction), and stimulation parameters.
2002	Blue Cross and Blue Shield, United States	Analysis of adverse events not included in review.
2001	Medical Services Advisory Committee, Australia	DBS-related adverse events related to the surgical procedure (e.g., lead dislodgement and hematoma), functional status (e.g., dysarthria and transient paraesthesia), and cognitive or behavioural function (e.g., confusion and disorientation). Estimates of incidence, however, are uncertain.

Summary of Medical Advisory Secretariat Review

The systematic literature search by the Medical Advisory Secretariat Review yielded 2 RCTs and 16 level 3a studies for the 3 conditions combined. The 2 RCTs were specific to patients with PD, as were 12 of the 16 level 3a studies. The review on essential tremor gave rise to 3 level 3a studies, and that for primary dystonia resulted in the inclusion of 1 study. The review of the evidence is presented separately for each of the 3 conditions of interest.

Parkinson's Disease

The Medical Advisory Secretariat included 2 RCTs and 12 non-RCTs with contemporaneous controls on Parkinson's disease (Table 4). The RCTs have 2 study parts each. The first part of the publication was based on the randomization component; it is included here as an RCT. The second part included a non-randomized prospective pre-post design; it is included here as level 3a evidence.

The merits of the RCT include the minimization of selection bias to either intervention. Selection bias may occur when a characteristic of the patient is associated with the outcome of interest, and either

through self-selection (the patient agrees to or requests one procedure over the other) or physician referral, may alter the observed effect of the intervention. Another advantage of having patients act as their own controls is that it may minimize a confounding bias, particularly for unknown factors. The disadvantage of not having a (separate) control group is that it does not allow investigators to examine the effect of treatment relative to standard care.

Table 4: Quality of Evidence of Included Studies for Parkinson's Disease

Study Design	Level of Evidence	Number of Eligible Studies
Systematic reviews of RCT	1a	0
Large RCT*	1b	1
Large RCT unpublished but reported to an international scientific meeting	1(g)†	0
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	12
Non-RCT with historical controls	3b	—
Non-RCT presented at international conference	3(g)	—
Surveillance (database or register)	4a	—
Case series (multisite)	4b	—
Case series (single site)	4c	—
Retrospective review, modeling	4d	—
Case series presented at international conference	4(g)	—

*RCT refers to randomized controlled trial.
†g indicates grey literature.
— indicates not applicable.

Outcome Measures

Measures of short-term and long-term effectiveness of DBS in PD focus primarily on these outcomes:

- Changes in motor function as measured by the UPDRS III score
- Changes in ADL as measured by the UPDRS II score
- Percent reduction of daily drug intake as measured by L-dopa equivalent daily dose
- Percent of the waking day spent in good or poor function derived from the UPDRS IV (question 39) score or daily diaries kept by patients.

Change in all measures was based on a comparison of absolute values at follow-up (in the phase after implantation, or post-implantation), with baseline levels (before implantation, or pre-implantation). Percent change was estimated as the difference in post-implant to pre-implant measures, as a proportion of the baseline measure.

Randomized Clinical Trials – Level 1b and Level 2 Evidence

Two randomized controlled trials for DBS in PD were included in this review. Both used a double-blinded assessment protocol (patient and physician blinding), and had similar methodologies. Both trials,

as well as the level 3a evidence, were comprised of patients with similar functional disability; therefore, findings are comparable across studies with respect to baseline measures.

The randomization and motor function assessment occurred after the surgery. Patients were randomized to a post-implantation sequence of either DBS off first and then on, or DBS on first and then off. This form of randomization allowed investigators to examine the efficacy of DBS in both the on and off conditions and to examine any carry-over and period effects. The motor function assessment was conducted in the absence of medication, following a 12-hour drug and DBS washout period. It is important to note, however, that these assessments were conducted during the clinic visit, i.e. within a 24-hour period. Therefore, the time frame for the findings as derived from these studies is referred to in the conclusions as a 24-hour period.

The Deep Brain Stimulation for Parkinson's Disease Study Group (20) published results (level 1b evidence) of their RCT (prospective, double-blinded crossover study) in advanced PD patients from 18 centres. The study examined the effectiveness of bilateral DBS of the subthalamic nucleus or global pallidus in 96 and 38 patients, respectively. However, only stimulation of the subthalamic nucleus is reported here. Motor function was evaluated for subjects in both a double-blinded randomized component (after implantation only with DBS on and off) and open-label format (DBS on and off, and meds on and off at 6 months after implantation).

The results of the randomization component, presented in Figure 1, are as follows: the effect of DBS (in the meds-off condition) gave rise to significant changes in the UPDRS motor function scores, regardless of the off/on sequence of the stimulator ($P < .001$). Randomization also enabled investigators to look for a treatment and period effect, neither of which was significant ($P > .05$). The authors concluded that DBS of the STN is effective in reducing motor dysfunction in a 24-hour period in the meds-off condition.

In the open-label analysis (level 3a evidence) the effect of DBS on motor function was examined at 6 months after implantation relative to baseline in both the meds-off and meds-on conditions. For DBS of the subthalamic nucleus in the meds-off condition (i.e., representing the absence of drug benefit for the patient), the preoperative baseline motor function score (SD) of 54.0 (15.1) was improved by 51.3% ($P < .001$) at 6 months, based on the UPDRS. In the meds-on condition (i.e., representing the state of maximal benefit of the drug), a 25.8% improvement in motor function from baseline at 6 months (mean [SD] UPDRS score: 23.6 [10.2]) was significant ($P < .001$), yet less pronounced than in the meds-off condition.

These findings suggest that DBS of the subthalamic nucleus is effective in the control of motor dysfunction associated with a baseline UPDRS measure of 54, both in the meds-off and meds-on conditions, as assessed over 24 hours, and assuming continuous stimulation and drug therapy for 6 months (Figure 2).

An additional benefit was the reduction of the mean daily dose of L-dopa equivalents from 1218.8 mg (SD, 575 mg) at baseline to 764.0 mg (SD, 507 mg) ($P < .001$) at 6 months for DBS of the STN only.

Figure 1: RCT Results for Deep Brain Stimulation of the Subthalamic Nucleus, Outcome of Motor Function, Deep Brain Stimulation Study Group (n = 91)

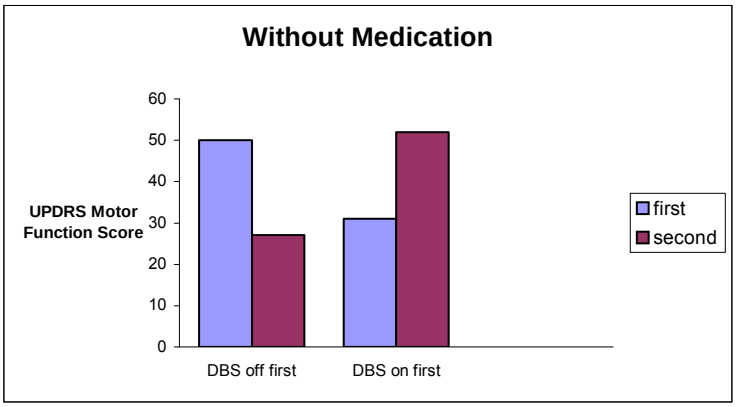
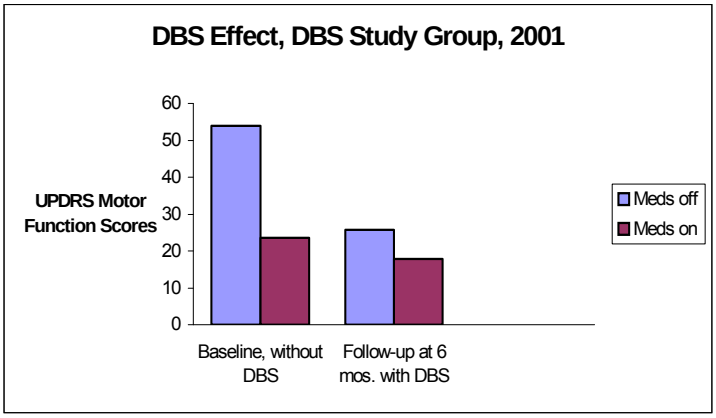


Figure 2: Stimulation of the Subthalamic Nucleus, Comparison of Baseline Motor Function Measures to 6 Months Follow-up (n = 91)



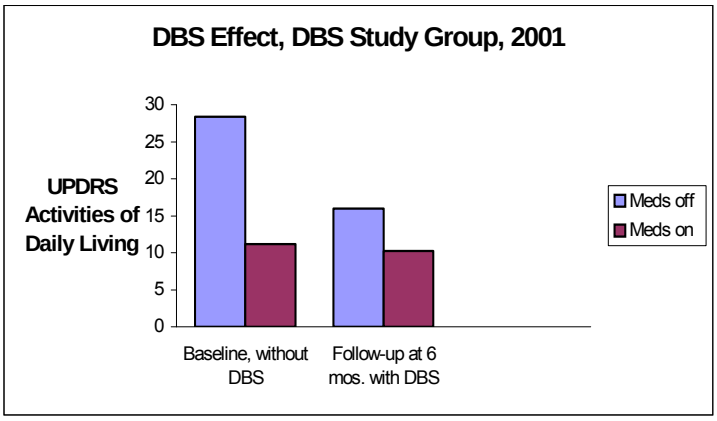
In examining the effect of DBS and medication combined, the investigators observed a significant interaction ($P < .001$) for DBS of both the subthalamic nucleus and globus pallidus, which they referred to as a synergistic effect on motor function scores. In practice, this finding suggests that while DBS alone (i.e., in the meds-off condition) allows for a reduction in the UPDRS motor score from 54.0 before the implantation to 25.7 at 6 months, combining DBS with medication (at about 50% of the baseline dose) confers a further improvement of motor function for a mean UPDRS score of 17.8. This synergistic effect, found for stimulation of both brain sites, should be interpreted cautiously, however, because it has not been found consistently across studies. (Personal communication with clinical expert, February 2005)

To examine the effect of disease progression on these results, UPDRS scores at baseline in the meds-off condition were compared to the meds-off, DBS-off condition at 6 months. This comparison revealed no change in motor function scores for stimulation, which suggests that the observed effect of DBS was not further affected by disease progression in this short-term follow-up study.

Of note, these measures of motor function during the clinic visit are based on an arbitrary time period (on/off stimulation and on/off meds in an experimental setting) and do not reflect the complications of the wearing off of the drug and the motor fluctuations experienced throughout the day. The potential of DBS to stabilize motor fluctuations is best assessed using measures more representative of all-day function, such as ratings of ADL, and more specifically, the percent of the waking day spent in good function.

Improvement in ADL at 6 months after implantation compared with baseline was significant in the meds-off condition for DBS of the subthalamic nucleus (Figure 3). The difference in baseline measure (mean [SD] UPDRS score: 28.4 [8.7]) and follow-up at 6 months (mean [SD] UPDRS score: 16.0 [8.0]) in the meds-on condition, however, was not significant (P=0.93). This data suggests that DBS is effective in the control of motor dysfunction, particularly symptoms associated with the minimal effect of the drugs.

Figure 3: Stimulation of the Subthalamic Nucleus, Comparison of Baseline Measures of Activities of Daily Living to 6 Months Follow-up



An important measure in assessing motor function throughout the day is the percentage of the waking day spent in good function (i.e., in an "on" state without dyskinesia). In the study, the patient recorded this information at 30-minute intervals during the 2 days before going to the clinic, both pre-implantation (baseline) and at 6 months. The daily diaries captured information on time spent in poor mobility ("off" state), in good mobility with dyskinesia ("on" state with dyskinesia), and in good mobility without dyskinesia, the optimal state.

The mean difference in percent of the waking day spent in good mobility without dyskinesia rose significantly ($P < .001$) from 27% at baseline to 74% at 6 months. For the average patient, this translates into good motor function without dyskinesia for about three-quarters of the waking day for those receiving stimulation of the subthalamic nucleus at 6 months, compared with no stimulation at baseline.

More recently, Rodriguez-Oroz et al. (21) reported similar results. Considered level 2 evidence because of its small sample size (n = 10), this study had an initial randomization component as outlined in the DBS Study Group Study, with patients randomized after implantation to either DBS on first and then off, or vice versa. Baseline motor function scores were similar to those of the previous study, suggesting a similar baseline severity of motor dysfunction in the 2 studies.

The double-blinded comparison (level 2 evidence) showed that bilateral DBS of the subthalamic nucleus was effective (P =.04) over the 24-hour study period in the off-medication state, for an improvement of about 40%. Results of the open-label component of this study, which had a follow-up of 4 years, found a significant improvement in UPDRS motor function that was sustained to 4 years postoperatively (P < .03). These findings provide level 3a evidence that bilateral DBS of the subthalamic nucleus is effective up to 4 years.

Non-Randomized Clinical Studies – Level 3a Evidence

Most studies included in this assessment were non-randomized, prospective, pre-post studies with contemporaneous controls (level 3a evidence). They were based on a series of patients who had DBS surgery, and for whom the baseline measures of motor function, ADL, percent of the waking day spent in good function, and/or the daily L-dopa dose, were compared to follow-up measures after implantation. Thus, these patients served as their own controls.

The outcomes of interest were measured at baseline and follow-up. At baseline, before implantation, the patient arrived in the clinic after an overnight, 12-hour withdrawal from medication. He or she was tested first without medication (meds-off condition) and then after taking L-dopa (meds-on condition). After DBS surgery, patients were assessed after a drug and DBS overnight washout period. The assessment at follow-up included each of the 4 test conditions

- Medication off and DBS off (meds off/DBS off)
- Medication off and DBS on (meds off/DBS on)
- Medication on and DBS off (meds on/DBS off)
- Medication on and DBS on (meds on/DBS on)

The data were analyzed by comparing values before and after implantation, reported separately for the meds-off and meds-on conditions. As indicated, the meds-off comparison allows for the examination of DBS in the absence of medication and is intended to represent patients in their worst state, that is, one in which they are having no benefit from their drugs. The meds-on condition measures the effect of DBS in a state in which the patient is experiencing the maximal benefit from the drug. Ideally, this comparison allows for the estimation of the effect of DBS beyond that of medication, assuming that the drug dosage and the extent of disease progression were the same at the preoperative and postoperative assessments.

However, with stimulation of the subthalamic nucleus, the daily preoperative dosage of the drug is reduced considerably early on after the surgery; thus, the postoperative assessment combines the effect of DBS, disease progression, and the effect of the reduced medication dosage. The main issue with these comparisons, particularly in the absence of additional data on confounding variables, is that it is not possible to distinguish the benefit of DBS from that owing to the reduced drug dosage.

The follow-up for the studies in this review ranged from 6 months to 5 years. In this report, short-term effects are defined as those that occur within a follow-up of less than 12 months, whereas long-term effects are based on follow-up periods of 12 months or more. In the longer-term studies, the sample size diminishes with time. Therefore, in studies of longer follow-up, data are presented (in Table 5) for the year in which the loss due to follow-up is minimized rather than the final reported follow-up; this was intended to eliminate bias that might result from higher rates of losses due to follow-up. Details of the 12 studies reviewed are in Table 5.

Table 5: Summary of Studies Included as Level 3a Evidence*

Author, Year, Country Mean Follow-up, Months	Patient, Intervention, and Entry Criteria Information	Motor Function Scores, Mean (SD)	Findings†
Krause, 2004 (22) Germany Follow-up: 29.8 (range, 23–55) 9/27 followed-up 3+ years	N = 27 PD, Bilateral DBS of STN CAPIT protocol (off state Hoehn & Yahr >2.5), and severe drug effects Mean age: 57.7 years(range, 44–72) Mean PD duration: 14.4 years	UPDRS III: motor function, UPDRS II: ADL. Outcomes: tremor, akinesia, rigidity, posture, reduction in meds. **Motor function, preop and at last follow-up (mean, 30 mos):** **Preop** **Postop** **Off meds** 59.8 37.0 **On meds** 22.0 25.0	**Off meds:** UPDRS III: improved 44% from baseline ($P < .05$) UPDRS II: improved 17% ($P < .03$); DBS worsened speech and swallowing. Time "on" without dyskinesia increased by 70%. **On meds:** UPDRS III: No significant change in motor function. Speech improved with meds (not DBS). **Off meds/off DBS:** UPDRS III worsened, suggestive of disease progression. Tremor suppression better with STN than meds ($P < .05$). No significant change in postural stability. **Reduction in meds:** 39% at 12 mos, 30% at 30 mos ($P < .05$) (lower than in other studies).
Russman, 2004 (23) Switzerland Follow-up: < 60 yrs: 22.4 60–70 yrs: 17.5 70+ yrs: 14.5 range, 6–48	N = 52 PD, Bilateral STN DBS. (42 agreed to DBS off in meds-off state) L-dopa challenge: 25% improvement on UPDRS. No. patients by age: < 60 yrs: 15 60–70 yrs: 24 70+ yrs: 13:. N = 42 accepted "off DBS" condition.	UPDRS I to IV, Hoehn & Yahr scores. Outcomes: axial signs, bradykinesia, rigidity and tremor, reduction in meds **Off meds:** **Age** **Preop** **Postop** < 60 yrs: 46.5 (12.9) 17.5 (9.3) 60–70 yrs: 45.5 (15.8) 28.7 (11.2) > 70 yrs: 48.9 (12.3) 38.1 (13.4) **On meds:** **Age** **Preop** **Postop** < 60 yrs: 23.3 (6.3) 18.1 (9.5) 60—70 yrs: 25.1 (10.8) 25.5 (8.6) > 70 yrs: 26.6 (10.1) 33.5 (12.6)	**Off meds:** Compared with baseline, motor function improved in all ages ($P < .05$), but less in those 70+ yrs, leading to lower reduction of meds. Axial signs worsened after DBS in 70+ yrs, unchanged in younger pts. **On meds:** motor function worsened in 70+ yrs (more meds) compared to significant improvement in < 60 yrs. ADL unchanged for younger groups, worsened by 40% ($P < .001$) in 70+ yrs. *No reporting of "on/off" time duration.* **Reduction in meds** (L-dopa and agonists): at last follow-up: 49% for 70+ yrs, with 5 of 13 pts requiring no meds postop; 74% for < 70 yrs ($P < .01$). **Conclusion:** Motor function and dyskinesia improved with DBS in 70+ yrs, similar to pts < 70 yrs; therefore, older age group eligible for DBS.

Author, Year, Country Mean Follow-up, Months	Patient, Intervention, and Entry Criteria Information	Motor Function Scores, Mean (SD)	Findings†
Kleiner-Fisman, 2003 (24) Canada Follow-up: Median, 24 range, 12–52 11/25 followed-up 2+ yrs 9/25 followed-up 3+ yrs	N = 25 PD, Bilateral DBS of STN. CAPIT protocol, and at least 1 year of follow-up data. Mean (SD) age: 57.2 yrs. (11.7) Mean (SD) PD duration: 13.4 yrs. (4.3)	UPDRS III: motor function, UPDRS II: ADL, and combined UPDRS. Outcomes: Tremor, bradykinesia, rigidity, axial symptoms, reduction in meds **UPDRS motor function at 1 year:** **Preop** **Postop** **Off meds** 50.1 (12.3) 24.6 (7.3) **On meds** 22.8 (9.7) 19.4 (7.8)	**Off meds:** At 1 yr, combined UPDRS 42% (CI, 35–49%) improvement relative to baseline; motor function improvement of 48% (CI, 42–55%), ADL improved by 28% (CI. 13–43%). Despite improvement from baseline, worsening of motor function over time (*P* = .01), though not on ADL subscores (*P* = .19) or for dyskinesia (*P* = .08). **On meds:** At 1 yr, no change in motor function with DBS (*P* > .05). Off-time duration: reduction at last follow-up (*P* < .001). **Reduction in meds:** Mean of 36% (CI, 22–50%) over study period, 38% (CI, 25–50%) at 1 yr. **Conclusion:** Sustained reduction in motor disabilities, meds required and dyskinesias at 2 yrs.
Krack, 2003 (25) France Follow-up: 5 yrs (n = 42)	N = 49 PD, Bilateral DBS of STN. Drug-refractory PD, <70 yrs., no dementia, surgical contraindications, psychiatric illness. Mean (SD) age: 55 (7.5) yrs Mean (SD) PD duration: 14.6 (5.0) yrs	UPDRS III: motor function, UPDRS II: ADL, Schwab & England Scale. Outcomes: motor function (total, tremor, rigidity, akinesia, speech, postural stability, gait); ADL (total, writing, freezing of gait), reduction in meds **UPDRS motor function, preop and postop at 5 yrs:** **Preop** **Postop** **Off meds** 55.7(11.9) 25.8 (12.3) **On meds** 14.3 (7.0) 21.1 (12.2) **UPDRS motor function, postop at 1 yr. and at 5 yrs:** **Preop** **Postop** **Off meds** 19.0 (11.9) 25.8 (12.3) **On meds** 11.4 (8.9) 21.1 (12.2)	**Off meds:** At 5 yrs: baseline total motor function improved 54% (*P* < .001); UPDRS ADL improved 49% (*P* < .001). Only speech did not improve (*P* > .05). Schwab & England ADL: Independence at 5 yrs. relative to dependence at baseline. Comparing yr 1 to yr 5: ADL and total motor function, including akinesia, speech, gait worsened (*P* < .001 for each). **On meds:** Only dyskinesia improved at 1 yr (*P* < .05). At 5 yrs: total motor function, akinesia, speech and gait improved (*P* < .05). Tremor, rigidity, postural stability not improved (*P* > .05 for each). Yr 1 to yr 5: ADL and total motor function, including akinesia, speech, postural stability, gait worsened (*P* < .001 for each). **Duration of dyskinesia:** at 5 yrs decreased 71% from baseline (*P* < .001). **Reduction in meds, duration and severity of LID:** significant at 5 yrs from baseline (*P* < .001 each). **Conclusion:** marked improvements in motor function over 5 years, though decreases over time.

Author, Year, Country Mean Follow-up, Months	Patient, Intervention, and Entry Criteria Information	Motor Function Scores, Mean (SD)	Findings†
Pahwa, 2003 (26) United States Follow-up: 27.8 33/35 at 12 mos; 19/35 at 29 mos	N = 35 PD, Bilateral DBS of STN. Two or more PD symptoms; meds-resistant fluctuation or tremor, <80 yrs; no sig. medical history, cognitive or psych illness; min. 1 yr follow-up Mean age: 58.4 yrs Mean PD duration: 11.8 yrs	UPDRS III: motor function, UPDRS II: ADL, Schwab & England Scale (ADL), Hoehn & Yahr scale. Outcomes: motor function, ADL, reduction in meds. **UPDRS motor function, preop and at 12 mos, n = 33:** **Preop** **Postop** **Off meds** 42.8 (9.8) 26.5 (11.6) **UPDRS motor function, preop and at 24 mos, n = 19:** **Preop** **Postop** **Off meds** 41.3 (8.4) 29.8 (13.1) **On meds** 26.2 (7.7) 22.8 (8.3)	**Off meds:** At 1 yr from baseline: 38.1% improvement in motor function; at 24 mos: improvement of 28% in motor function (*P* = .003) and 27% in ADL (*P* = .001). **On meds:** at 24 mos from baseline: no change in motor function (*P* = .11), or ADL (*P* = .08). "Off-state": from 44% at baseline to 17% of waking hours at 2 yrs. "Meds-on state": from 38% at baseline to 72% at 2 yrs. "Meds-on with dystonia": from 18% to 11% at 2 yrs. **Reduction in meds:** 57% in daily L-dopa dose. **Conclusions:** Significant motor function improvements with DBS. Device-related events common; required repeated surgeries.
Romito, 2003 (27) Italy Follow-up: 25.7 33/33 for 3 mos 13/33 for 36 mos	N = 33 PD, Bilateral DBS of STN. Advanced PD with meds-resistant motor fluctuations, Hoehn & Yahr ≥ III; no cognitive or psych illness, prior brain surgery, poor health. Mean (SD) age: 56.8 (7.1) yrs Mean PD duration: 13.8 (5.5) yrs	UPDRS III: motor function, UPDRS II: ADL, Schwab & England scale. Outcomes: motor function, ADL, reduction in meds. **UPDRS motor function, preop and at 12 mos, n = 25:** **Preop** **Postop** **Off meds** 59.6 (8.9) 29.9 (13.4) **On meds** 24.2 (8.6) 22.1 (10.7)	**Off meds:** At 12 mos, 49.9% improvement in motor score; 66.3% improvement in ADL; Schwab & England scale improved *by 183.8%* (*P* < .001 for each). **On meds:** At 12 mos, no significant change in motor function, or ADL (Schwab & England scale). ADL (UPDRS) improved by 31.4%. Greater improvements at 36 mos, though n = 13. Dyskinesia duration (baseline) decreased by 80.3% (*P* < .001) at last visit. Off-period duration decreased by 94.2% (*P* < .001). **Reduction in meds:** From baseline, 66.1% at 12 mos, 64.4% at 24 mos, 51.6% at 36 mos. (*P* < .001 for each). **Conclusion:** Effectiveness of DBS retained during yrs 2 and 3 postop, without increase in energy delivered.
Ostergaard, 2002 (28) Denmark	N = 26 PD, Bilateral DBS of STN. CAPSIT-PD, Medically	UPDRS: motor function, ADL and complications, Hoehn & Yahr staging, Schwab & England scale. Outcomes: motor function, ADL, L-dopa reduction.	**Off meds:** At 3 mos (double-blinded evaluation): motor function improvement of 57% (*P* < .05). At 12 mos: 64% improvement in motor function and ADL (*P* < .05).

Author, Year, Country Mean Follow-up, Months	Patient, Intervention, and Entry Criteria Information	Motor Function Scores, Mean (SD)	Findings†
Follow-up: 12	intractable motor fluctuations, other serious conditions. Mean age: 59 (8) yrs (range, 30–75) **[AU: OK?]** Mean PD duration: 15 (5) yrs	**UPDRS motor function, preop and at 12 mos, n = 26:** **Preop** **Postop** **Off meds** 51.3 (12.1) 18.3 (10.0) **On meds** 23.5 (15.8) 10.7 (7.2)	**On meds:** Significant improvement in motor function with DBS relative to baseline ($P < .0001$). No change in UPDRS ADL at 12 mos. Synergistic effect of DBS and meds. Dyskinesia duration: reduction of 86%. Off-period duration: reduction of 83% ($P < .05$). **Reduction in meds:** 22% at 12 mos. Compared to other studies: lowered reduction likely due to smaller preop doses.
Tavella, 2002 (29) Italy Follow-up: 2 yrs 39/47 for 3 mos 21/47 at 1 yr 7/47 at 2 yrs	N = 47 PD, Bilateral DBS of STN Mean age: 62.8 yrs Mean PD duration: 15.6 yrs	CAPIT protocol, baseline Hoehn & Yahr = 4. Outcomes: motor function, reduction in meds Data presented as % change.	**Off meds:** 56.4% improvement in motor function at 3 mos, 58.2% at 1 yr, 63.4% at 2 yrs. Drug-induced dyskinesias reduced by 80% after 1 yr, 90% after 2 yrs. ADL improved 58% at 3 mos, 57% at 1 yr, 55% at 2 yrs ($P < .05$ for each). **On meds:** No data provided. *Off-time duration not reported.* **Reduction in meds:** Compared to baseline, 73% at 1 yr (6 pts no longer taking L-dopa), 81% at 2 yrs ($P < .05$).
Valldeoriola, 2002 (30) Spain Follow-up: 18	N = 26 PD, Bilateral DBS of STN Group A: No meds postop (n = 10) Group B: Do require meds postop (n = 16).	UPDRS III: motor function, Schwab & England scale: ADL, Hoehn & Yahr staging scale. Outcomes: motor function, reduction in meds. **Group A: UPDRS motor function, preop and at 18 mos, n = 10:** **Preop** **Postop** **Off meds** 49.0 (13.6) 21.6 (14.2) **On meds** 19.2 (6.4) 21.6 (14.6) **Group B: UPDRS motor function, preop and at 18 mos, n = 16:** **Preop** **Postop** **Off meds** 49.8 (12.7) NA **On meds** 19.3 (7.9) NA	Group A: **Off meds/off DBS:** UPDRS worsened by 17.5% for tremor, but not rigidity, bradykinesia, or axial symptoms. **Off meds/on DBS:** 65% improvement compared with off-meds baseline. Group B: **On meds/on DBS:** 55% improvement compared with off-meds baseline, but non-significant worsening compared to on-meds baseline. *Off-time duration not reported.* **Reduction in meds:** **Group A:** Not relevant. **Group B:** 47% (25%) decrease in preop dose.
Vesper, 2002 (31) Germany	N = 38 PD, bilateral DBS of STN	UPDRS III: motor function, Schwab & England scale: ADL, Hoehn & Yahr staging scale.	**Off meds:** Significant improvement in UPDRS motor function at 12 mos. ($P < .05$). Hoehn & Yahr and ADL also significantly improved in off-state at 12 mos ($P < .001$).

Author, Year, Country Mean Follow-up, Months	Patient, Intervention, and Entry Criteria Information	Motor Function Scores, Mean (SD)	Findings†
Follow-up: 1 yr		Outcomes: motor function, ADL, reduction in meds. **UPDRS motor function, preop and at 12 mos, n = 25:** **Preop** **Postop** **Off meds** 59.6 (8.9) 29.9 (13.4) **On meds** 24.2 (8.6) 22.1 (10.7)	**On meds:** Significant improvement in UPDRS motor function at 12 mos ($P < .05$). Off-time duration reduced by 35% (range: 10%–60%) from 14.6 hrs to 6 hrs per 24 hrs. **Reduction in meds:** Mean, 53%.
DBS Study Group, 2001 (20) 18 centres Follow-up: 6	N = 96, bilateral DBS of STN N = 38, bilateral DBS of GP Unblinded portion included here as level 3a evidence.	UPDRS III: motor function, UPDRS II: ADL. Outcomes: motor function, ADL, reduction in meds., % time in "on-state". **UPDRS motor function, preop and at 6 mos, DBS of STN, n = 96:** **Preop** **Postop** **Off meds** 54.0 (15.1) 25.7 (14.1) **On meds** 23.6 (10.2) 17.8 (12.1) **UPDRS motor function, preop and at 6 mos, DBS of GP, n = 38:** **Preop** **Postop** **Off meds** 50.8 (11.6) 33.9 (12.3) **On meds** 24.1(14.6) 16.5 (9.5)	**Off meds:** Median % change at 6 mos: 51.3% improvement in motor function with DBS of STN; 33.3% with DBS of GP. ADL improved significantly. **On meds:** Median % change at 6 mos: 25.8% improvement in motor function with DBS of STN; 26.8% with DBS of GP. Significant change in ADL at 6 mos only with DBS of GP. UPDRS subscores improved ($P < .05$) for DBS-STN but not DBS-GP. "On-time" without dyskinesia, for DBS-STN: from 27% to 74% ($P < .001$), for DBS-GP: from 28% to 64% ($P < .001$). **Reduction in meds:** DBS-STN: Significantly decreased from baseline (from 1218 to 764 mg) ($P < .001$). DBS-GP: No change from baseline (1090 to 1120 mg at 6 mos).

*ADL indicates activities in daily living; LID, levodopa-induced dyskinesia; NA, not available; pts, patients; preop, preoperative; postop, postoperative; CI, 95% confidence interval; SD, standard deviation.
†*P* rounded to 2 decimal places, unless stated otherwise.

A summary of the evidence suggests that DBS resulted in a significant improvement in motor function in the range 22% to 71%, as measured by the UPDRS. The follow-up periods in these studies ranged from 6 months to 5 years. This observation was specific to the meds-off condition (with DBS and without medication at follow-up, compared with neither medication nor DBS at baseline). The improvement in motor function in the meds-on condition (with DBS and medication at follow-up compared with medication and no DBS at baseline) was less pronounced. Across all studies, improvement in motor function ranged from 0% to 54% in the meds-on condition, with most of the studies showing a change in motor function from baseline that was not statistically significant.

Of most importance, however, was that the daily dose of L-dopa at follow-up was about 50% of that at baseline. Thus, the similarity in motor function at baseline and follow-up is supportive of DBS as an adjunctive therapy. This decrease in daily drug intake is important in that it will likely result in the reduction of motor dysfunction associated with the higher doses.

Of further importance was the percent improvement in the percent of the waking day spent in good function without dyskinesia, which ranged from 54% to 94% across studies reporting this outcome.

Adverse Events in Parkinson's Disease

Data on adverse events, as reported in the studies included in this review, are listed in Table 6. These events may be due to DBS, the procedure or progression of disease, and when reported, information on the permanency of the event has been provided. Serious adverse effects include permanent motor dysfunction, intraventricular or intracranial hemorrhage, and cognitive impairment. Four deaths have been reported, 3 of which occurred during a 5-year study (22;25) and 1 during a 30-month follow-up (22;25), but it is unclear if they are related to DBS. These events are based on short-term and longer-term follow-up up to 5 years only.

Expert opinion suggests that the rate of serious adverse effects may be as high as 8%, but that it falls to about 4% in multidisciplinary expert centres. (Personal communication with clinical expert, February 2005)

A review of adverse events indicates that the risk of hematoma (subdural, subarachnoid, intraventricular, or intracerebral) is relatively low, though not insignificant. (32) The rate of hemorrhage is cited as 3% to 5% per patient for a bilateral procedure. (20) A hemorrhage, while often clinically silent, may cause long-term disability or even death. Adverse cognitive or behavioural effects include severe depression and suicide attempts. (33;34) Patients should also be aware that sudden withdrawal of DBS due to the switching off or malfunction of the device poses a theoretical risk of developing a neuroleptic malignant-like syndrome; furthermore, diathermy in the region of the device may result in severe neurologic damage. (32)

Table 6: Reported Adverse Events and Complications for Deep Brain Stimulation in Parkinson's Disease

Author, Year	Reported Adverse Event/Complication	Number of Patients (%)
Krause, 2004 (22)	Progressive postural instability Intraventricular hemorrhage Worsening of preop dysphagia, subsequent suffocation Pneumonia Transient hyperhidrosis Moderate dysarthria Lasting hyperkinesias Transient dysesthesias on DBS activation	1 1 1 1 1 3 2 most patients
Rodriquez-Oroz, 2004 (21)	Dementia with hallucinations Some degree of cognitive impairment Mini-mental score = 24, severe disequilibrium, urinary incontinence Mini-mental score=28, moderate depression Severe dysarthria Recurrent subcutaneous erosion, skull infection 3-4 yrs, postop Battery replacement after 36 – 52 mos. (mean=46 mos.)	1 2 1 1 1 1 19
Russman, 2004 (23)	**Over 70:** Leads repositioning Transient confusional states Connection wound dehiscence Delayed infection **Under 70:** Leads repositioning Air embolus Seizure Panic attack Transient confusional states Connection wound dehiscence	 1 3 1 1 1 1 1 1 4 1

Author, Year	Reported Adverse Event/Complication	Number of Patients (%)			
Kleiner-Fisman, 2003 (24)		Resolved	Persistent Event		
	Speech difficulty	6 (24)	3 (12)		
	Cognitive decline	5 (20)	4 (16)		
	Mood changes	4 (16)	2 (8)		
	Postop confusion	2 (8)	0		
	Hypersexuality	1 (4)	1 (4)		
	Scalp cellulitis	3 (12)	0		
	Scalp electrode erosion and cellulitis, Required skin graft	1 (4)	0		
	Worsened gait or balance	1 (4)	0		
	Persistent paresthesia	1 (4)	0		
	Tonic face contraction	1 (4)	0		
	Eyelid opening apraxia	1 (4)	1 (4)		
	Device turned off spontaneously	1 (4)	0		
	Electrode suboptimally positioned; required repositioning	1 (4)	0		
Krack, 2003 (25)		**Postop: first 3 mos, n = 49**		**From 3 mos to 5 yrs., n=42**	
		Transient	**Permanent**	**Transient**	**Permanent**
	Related to procedure				
	Ballism	1	0		
	Asymptomatic bleeding detected on MRI	8	0		
	Intracerebral hemorrhage	0	2		
	Head trauma (fall in hospital)	0	1		
	Contusion	3	0		
	Dementia	0	2		
	Delirium	12	0		
	Seizures	2	0		
	General health complications	6	0		
	Wound healing problem	4	0		
	Related to device				
	Skin erosion with infection	1	0		
	Stimulator repositioning	2	0	1	0
	Related to DBS or disease				
	Disabling dyskinesia	–	4	5	2
	Weight gain	–	41 (max, 5kg)	0	39 (max, 16kg)
	Eyelid-opening apraxia	0	15	0	8
	Depression	1	0	7	0
	Apathy	0	1	2	5
	Impulsive aggressive behaviour	1	0		
	Hypomania	4	1		
	Tetanic muscle contraction			0	2
	Dysarthria			2	2
	Hilarity			1	0
	Hallucinations			2	3
	Psychosis			1	0
	Dementia			0	3
	Suicide attempts			3	0
	Death during follow-up: 3				

Author, Year	Reported Adverse Event/Complication	Number of Patients (%)
Pahwa, 2003 (26)	Postoperative seizures within 24 hrs Postop Infection Related to device	 3 of 70 procedures (4.3%) about 4.3% higher than in other studies, but not reported
Romito, 2003 (27)	**Increased weight** **Transient** Increased sexuality Manic psychosis Seizure **Long-lasting (**unresponsive to stimulation withdrawal for few hours**)** Hypophonia Hypophonia and dysarthria Eyelid opening apraxia Worsening of depression Psychic akinesia Limb dystonia Bilateral buccinator spasm **Stimulation dependent (**responsive to stimulation withdrawal for few hours**)** Paresthesias Ballic-choreic dyskinesias Blepharospasm Diplopia Monolateral buccinator spasm **Events occuring during surgical procedure** Transient intraoperative psychosis Lead migration Subarachnoid hemorrhage **Device failure** Unexplained switching-off Sudden end of battery life	**Adverse events observed in 33 patients:** 33 (mean increase of 11.1%, $P < .001$) 4 2 1 12 5 4 3 2 1 1 10 3 2 2 1 7 2 1 3 4
OStergaard, 2002 (28)	Dysarthria Cognitive function – worsening of short-term memory	Number not stated 2
Tavella, 2002 (29)	Transient mental confusion Hypophonia Transitory eye opening apraxia Thrombophlebitis Subcutaneous infection	7 of 47 pts. 2 1 1 1
Valldeoriola, 2002 (30)	 Severe dysarthria and/or mild Dysphagia Transient mood change/depression Weight gain	**Group A:** **Group B:** 1 3 2 3 1 (15 kg) 1 (12 kg)

Author, Year	Reported Adverse Event/Complication	Number of Patients (%)	
Vesper, 2002 (31)	Infection, leading to system removal	2 (5%)	
	Permanent worsening of previous Depressive state	2 (5%)	
	Developed progressive dementia	2 (5%)	
DBS Study Group, 2001 (20)		**Number events, DBS of STN**	**Number events, DBS of GP**
	Related to procedure:		
	Intracranial hemorrhage	3	4
	Hemiparesis secondary to hemorrhage	3	3
	Seizures	3	1
	Infection	4	0
	Improper lead placement	2	0
	Brachial plexus injury	1	0
	Confusion	1	0
	Dysarthria	0	1
	Paralysis (nonhemorrhagic)	1	0
	Pulmonary embolus	1	0
	Related to device:		
	Migration	3	2
	Infection	3	1
	Lead break	1	1
	Seroma	1	1
	Erosion	1	0
	Abnormal healing	1	0
	Intermittent function	1	0
	Related to stimulation:		
	Dyskinesia	2	3
	Diplopia	2	0
	Dystonia	0	2
	Abdominal pain	0	1
	Accidental injury	1	0
	Dysarthria	1	0
	Headache	1	0
	Paresthesia	1	0

Summary of Findings on Deep Brain Stimulation for Parkinson's Disease

- There is level 1b evidence that bilateral DBS of the subthalamic nucleus is efficacious in the 24-hour study period (DBS Study Group). (20)
- There is level 3a evidence for the following:
    - Bilateral DBS of the subthalamic nucleus is effective in the control of advanced PD symptoms for at least 5 years, based on measures of motor function, activities in daily living, percent of the waking day spent in good function without dyskinesia, and reduction in daily drug intake.
    - The effectiveness is apparent in the meds-off and meds-on conditions.
    - At least one study shows synergism between DBS and meds at 6 months after implantation.
    - The use of DBS of the subthalamic nucleus allows for a daily drug intake reduction of about 50%.

Deep Brain Simulation for Movement Disorders Other than Parkinson's Disease: Essential Tremor and Primary Dystonia

The search for health technology assessments for DBS in conditions other that PD gave rise to one report by the Wessex Institute (35) in 2001.

The Wessex Institute, United Kingdom (35)

Deep Brain Stimulation for Movement Disorders Other than Parkinson's Disease

Objective: To determine the effects of DBS in people with movement disorders other than PD.
Subjects: Patients with movement disorders that are refractory to medical treatment.
Comments: Includes review of evidence for unilateral and bilateral DBS.

Studies Included	Findings	Conclusions
➢ 1 RCT* (variety of conditions) ➢ 20 case series (5 on essential tremor, 1 on dystonia, 14 on variety of conditions)	➢ Due to methodological limitations, limited evidence for the use of DBS in essential tremor, and inconclusive evidence for DYT1 dystonia. ➢ No evidence for DBS* in other non-PD* movement disorders.	➢ Does not support the use of DBS for essential tremor, dystonia, and multiple sclerosis.

*DBS indicates deep brain stimulation; PD, Parkinson's disease; RCT, randomized controlled trials.

This health technology assessment is the only one that the Medical Advisory Secretariat found on DBS in conditions other than PD. The single RCT examined the effect of DBS relative to thalamotomy in 13 patients with essential tremor, 10 with multiple sclerosis, and the remainder with PD (not included here). The results showed an improvement in a general measure of disability (Frenchay Activities Index) for DBS in essential tremor compared with thalamotomy, but there was no significant difference between procedures for patients with multiple sclerosis. The overall quality of studies was deemed poor. There were concerns over inadequate and inconsistent reporting of selection criteria, treatment techniques (e.g., unilateral and bilateral DBS were combined in some studies), adjunctive treatment, blinding of outcome assessment, and the content and validity of the measures of disability.

Data on safety included reports from the United States Food and Drug Administration Summary of Safety and Effectiveness (35), in which the rate of reported procedure-related adverse events was 28%. The most common complications were postoperative pain (7%), lead misplacement (6%) and migration (3%), intracranial hemorrhage (3%), infection (2.6%), skin erosion (1.9%) or hematoma (1.2%), and seizures (1.2%). However, the analysis of case series data from studies in the health technology assessment indicated that few procedure-related events were serious, but it cautioned that less frequent yet severe complications might not be captured in small studies.

Summary of Medical Advisory Secretariat Review for Studies on Essential Tremor and Primary Dystonia

Essential Tremor

Three level 3a studies (36-38) assessed the effectiveness of DBS in managing the symptoms of essential tremor (Table 7). All were specific to stimulation of the thalamus, with results combined for unilateral and bilateral stimulation in 2 studies. (37;38) The study by Koller et al. (36) were specific to unilateral stimulation.

Table 7: Quality of Evidence of Included Studies for Essential Tremor

Study Design	Level of Evidence	Number of Eligible Studies
Systematic reviews of RCT*	1a	0
Large RCT	1b	0
Large RCT unpublished but reported to an international scientific meeting	1(g)†	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	3
Non-RCT with historical controls	3b	—
Non-RCT presented at international conference	3(g)	—
Surveillance (database or register)	4a	—
Case series (multisite)	4b	—
Case series (single site)	4c	—
Retrospective review, modeling	4d	—
Case series presented at international conference	4(g)	—

*RCT refers to randomized controlled trial.
†g indicates grey literature.
— indicates not applicable.

The 3 studies examined the effects of DBS without medication. The follow-up period varied between studies, with an average of 40 months (36) in one study and 3 years (38) and 6 years (37) for the others. All 3 studies included patients only with essential tremor, with sample sizes of 52 (38), 37 (37), and 49 (36), although these decreased with increases in the follow-up period. In all studies, patients showed significant (P <.05) improvements in ADL and tremor as measured by the tremor rating scale (a 5-point Likert scale of tremor, ADL, and global disability). In the study by Koller et al., patients were evaluated blindly at 3 months, whereas the baseline and 12 month and each yearly assessment was conducted in an open fashion. There was no significant change in tremor from 3 months to the longer-term follow-up. (36)

Adverse Events in Essential Tremor

Data on safety reported in the 3 studies of DBS of the thalamus in essential tremor are shown in Table 8. Data on transient and ongoing (unresolved) adverse events were included. Three deaths were reported by Koller et al., although they state that these were from unrelated causes.

Table 8: Reported Adverse Events and Complications for Deep Brain Stimulation in Essential Tremor

Author, Year	Reported Adverse Event/Complication	Number of Patients (%)		
Putzke, 2004 (38)		**Unilateral (%)**	**Bilateral (%)**	
	Dysarthria	0 (0)	6 (27)	
	Disequilibrium	2 (9)	5 (23)	
	Paresthesia	3 (14)	1 (5)	
	Motor disturbance	1 (5)	2 (9)	
Sydow, 2003 (37)	**As reported for 19 pts**	**Reported events**	**Resolved**	**Ongoing**
	Related to stimulation			
	Paraesthesia		3	3
	Dysarthria	6	1	3
	Gait disorders	4	3	–
	Dystonia	3	–	1
	Local adverse symptoms	1		
	Headaches		–	2
	Head and chest pain	2	1	–
	Pain at pocket site	1	2	–
	Pain at connector site	2	1	–
	Local pain over pulse generator	1	1	–
	Related to surgery	1		
	Infection		2	–
	Erosion	2	2	–
	Skin irritation	2	2	–
	Subcutaneous hematoma	2	1	–
	Paresis	1	1	–
	Lead repositioning owing to	1	1	–
	unsatisfactory effect	1		
	Other adverse events			
	Fracture left wrist		1	–
	Fracture right clavicle	1	1	–
	Hardware related adverse events	1		
	End of battery life		5	–
	Loss of effect for other reasons	5	2	–
	Intermittent stimulation	2	1	–
		1		
Koller, 2001 (36)	**Surgical adverse events**	Adverse events in 25 patients at 40 months:		
	Asymptomatic bleeds	3		
	Postoperative seizures	1		
	Stimulation adverse events			
	Paresthesias	21		
	Headache	15		
	Paresis	6		
	Dysarthria	4		
	Nausea	4		
	Disequilibrium	3		

	Facial weakness	3
	Gait disorder	2
	Dystonia	2
	Mild attention/cognitive deficit	2
	Dizziness	2
	Hypophonia	1
	Anxiety	1
	Depression	1
	Syncope	1
	Drooling	1
	Vomiting during programming	1
	Device complications	
	Shocking sensation resolved with Programming	1
	Lead replacement due to loss of effect	6
	Lead replacement due to fracture	1
	Lead reposition due to loss of effect	2
	Lead reposition due to migration	1
	Extension wire replaced due to erosion	3
	IPG* replaced due to loss of effect	1
	IPG replaced due to shocking of arm	1
	IPG replaced due to battery replacement	2
	Entire system explanted due to loss of effect and thalamotomy performed at 29 mos after surgery.	1
	Number additional surgical procedures:	
	One	7
	Two	4
	Three	1
	Number of deaths: 3	

***** IPG, implantable pulse generator.

Summary of Findings for Essential Tremor

- There is level 3a evidence that DBS of the thalamus effectively controls tremor in essential tremor and Parkinson's disease. The longest duration of follow-up was 6 years.

Primary Dystonia

One study was identified (level 3a evidence) for the effectiveness of DBS in primary dystonia, and included based on a minimum sample size of 10.

Table 9: Quality of Evidence of Included Studies for Primary Dystonia

Study Design	Level of Evidence	Number of Eligible Studies
Systematic reviews of RCT*	1a	0
Large RCT	1b	0
Large RCT unpublished but reported to an international scientific meeting	1(g)†	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	1
Non-RCT with historical controls	3b	—
Non-RCT presented at international conference	3(g)	—
Surveillance (database or register)	4a	—
Case series (multisite)	4b	—
Case series (single site)	4c	—
Retrospective review, modeling	4d	—
Case series presented at international conference	4(g)	—

*RCT refers to randomized controlled trial.
†g indicates grey literature.
— indicates not applicable.

The French Dystonia Study Group (SPIDY) (39) recently published a prospective multicentre study on the effectiveness of bilateral DBS of the globus pallidus in 22 patients with primary dystonia (median age, 30 years; range, 14–54 years). All patients were evaluated at baseline and 12 months after implantation while taking their usual treatments. A significant improvement in motor dysfunction scores was observed at 1 year after the implantation, compared with baseline values on subscales of the Burke-Fahn-Marsden Dystonia Scale. On the dystonia total score, scores improved 54.6%, from 46.3 before the surgery to 21.0 at 12 months *(P* = .001). On the disability score, scores improved 44%, from 11.6 before the surgery to 6.5 at 12 months (*P* = .001).

At baseline, 20 of the 22 patients were receiving medical treatment: 14 were taking anticholinergic agents (mean dose trihexyphenidyl, 30 mg; mean dose tropatepine, 30 mg); 13, benzodiazepines; 5, antispastic drugs (dantrolene or baclofen); 5, tetrabenazine (mean dose, 89 mg); 2, levodopa; and 1 was taking bromocriptine. Five patients were taking analgesics; 5, antidepressants.

At 12 months after the implantation, 10 patients (from 14 at baseline) were taking anticholinergics at about 65% and 50% of the baseline dose for trihexyphenidyl and tropatepine, respectively. Two of 13 and 3 of 5 patients were no longer taking benzodiazepines and baclofen, respectively. Only 1 of the 5 patients on tetrabenazine were still taking it at follow-up, though the dose was reduced to about 30% of the baseline dose.

Five adverse events were reported in 3 patients. One patient experienced transient perioperative edema of the frontal lobe and a fractured lead (which leaked current) that was replaced; 1 had cutaneous necrosis of the scalp at the site of a resolved skin infection near the connector, and 1 had a localized skin infection that resolved and a hematoma near the neurostimulator.

Summary of Findings for Primary Dystonia

- There is level 3a evidence that bilateral DBS of the globus pallidus is effective for at least 12 months at reducing the motor dysfunction associated with primary dystonia.

Summary of Overall Findings of the Literature Review

- There is level 1b evidence that bilateral DBS of the subthalamic nucleus is effective in the short-term control of advanced parkinsonian symptoms, and there is level 3a evidence that the effect is sustained for at least 5 years.
- There is Level 3a evidence that DBS of the thalamus is effective in the control of tremor in patients with essential tremor and PD for at least 6 years.
- There is level 3a evidence that bilateral DBS of the globus pallidus is effective in the control of symptoms of primary dystonia for at least 1 year.

Economic Analysis

Ontario-Based Budget Impact Analysis

The estimates for the prevalence for each of the 3 conditions in Ontario are given below.

Parkinson's disease

Based on a population prevalence of 0.3% (2) and a population of 12 million, it is expected that there are 37,000 people with PD in Ontario.

Of these 37,000, only 10% to 15% are eligible for DBS (Personal communication with clinical expert, February 2005). This narrows the estimate to 3,700 to 5,550 people. Given that about 5% will consent to the procedure, this translates to 1,850 people with PD who are likely to undergo DBS surgery.

Essential tremor

A general population prevalence of 0.3% (9) translates to an estimated prevalence in Ontario of 37,000

people with essential tremor. Of these, 50% to 60% (18,500–20,500) will seek medical care, and 50% of these will have symptoms severe enough to be treated with drug therapy (range, 9,250–10,250). Sixty percent of these people (range, 5,550–6,150) will experience a suboptimal response and/or adverse effects to drugs, and 5% to 10% will be eligible for DBS, resulting in an estimate of 308 to 615 people.

Primary dystonia

The prevalence estimates used in this report are those for the general population, derived from a record-linkage study of cases from 1952 to 1980 in Rochester, Minnesota (13), and are as follows:

- Early-onset primary dystonia (younger than 20 yrs): 24 per million
- Late-onset primary dystonia (older than 20 yrs): 295 per million.

Based on a provincial estimate of 3 million people (2004 estimates (15)) younger than 20 years (2.2 million for those aged 0–14 years, and 0.8M million for people aged 15 to less than 20, based on a rate of 2.2 million per 14 years of age per year), and a rate of 34 per million, the expected prevalence of early-onset primary dystonia in Ontario is 102. The prevalence of late-onset dystonia (based on a population estimate of 12 million minus 3 million) in people older than 20 years is 2,655.

Accordingly, the number of people with primary dystonia in the province is about 2,757. Of these, about 75% with early-onset disease, and 5% to 10% with late-onset disease, may be eligible for DBS for a total of 208 to 340 people.

Hospitalization Costs

In the fiscal year of 2003, 57 hospital separations were identified that could have been associated with DBS. (A combination of ICD-10 diagnosis codes and CCI procedure codes were used. See Appendix 1 for a listing). In 2002, 61 hospital separations were identified. To determine the cost per case, the prospectively adjusted for complexity resource intensity weights (PAC-10 weights) were used based on a weight of 1.0 having a dollar value of $4,505 during 2003 (Personal communication, Ministry of Health and Long-Term Care, May 2005). The median PAC-10 weight in fiscal year 2003 was 2.57, resulting in an associated cost of $11,597 per hospital separation.[1] The total cost of hospitalization based on the most current volume of 57 hospital separations was $661,000.

Device Costs

The cost of a single-lead stimulation device is approximately $10,000, and a dual-lead device approximately $14,000. As a result, the total annual device costs based on current volumes would be in the range of $570,000 - $798,000. The implantable pulse generator device generally lasts 5 years, at which point it must be replaced at an additional cost.

[1] This is comparable to the £32,526 over 5 years-- including the cost of the procedure—calculated in a recent costing analysis from the United Kingdom. (40)

Professional (Ontario Health Insurance Policy) Costs

The course of treatment involves a neuropsychological assessment, the implantation of the device, and up to 8 postoperative visits with either a neurosurgeon or a neurologist.

Physician Costs: (Adjusted upward 2% to reflect the recent Ontario Medical Association agreement)

i. Neuropsychological assessment phase:
$128 (FSC A185): Specific neurocognitive assessment.

ii. Main Procedure:
$1,551 (FSC N124): Physician reimbursement for functional stereotaxy.

iii. Anesthetist costs:

Note: 11 base units + 1 unit for each 15 minutes in first hour + 2 units per 15 minutes thereafter.
39 units: number of average units billed (fiscal year 2003 for FSC N124).
$12.01: per unit fee for anesthetists

Total anesthetist costs: $468

iv. Follow-up assessment (up to 8 postoperative visits):

Any of the following codes can be used for follow-up:

$186 (FSC G547): Clinical Programming of Deep Brain Stimulator (DBS): One session
$158: (FSC G549): Additional Implantation site(s)[2]
$279: (FSC G548): Electrophysiological assessment of Deep Brain Stimulators.[3]
$128: (FSC A185): Neurology Consult
$25: (FSC A188): Neurology Partial Assessment
$102: (FSC A045): Neurosurgery Consult
$27: (FSC A044): Neurosurgery partial assessment

Assumption: One consult by each of neurosurgery and neurology plus 2 partial assessments by each in addition to a single device programming session and sometimes a electrophysiological assessment.

$676: total expected postoperative physician reimbursement ($182 + (75% x 155) + (14% x $273) + $125.00 + (2 x $24.65) + $100.00 + (2 x $26.00))

[2]Note: 51 of 70 (75%) received bilateral implantation (i.e., G547 & G549)

[3]Note: 70 patients had G547, 88 had G549, 51 had both codes, and 21 had G548—a total of 128 patients (70 + 88 + 21 -51 = 128). Since there were 121 distinct patients in fiscal year 2003 with these codes (some of which could be associated with implantations performed in previous fiscal years), 4 of 21 patients with G548 were not distinct. We therefore deduced that there were 17 distinct patients with G548. As a result: 17/121 patients (14%) had the code G548 (Physician Services Branch, Ministry of Health and Long-Term Care, February 2005).

Total Professional Costs Over One Year Course of Treatment:

$2,823: total professional medical fees per case (expected)

$161,000: total professional medical fees based on annual 57 DBS implantations.

In summary, the total cost (hospital, physician and device costs) per case would be $24,420 - $28,420 and for 57 annual procedures the total cost is in the range of $1.4 - $1.6 million.

Diffusion Pressure

Based on an estimate of 209 procedures per year (derived from diffusion data from the United States), the hospitalization costs would be $2.3 million, the OHIP costs would be $591,000, and the device costs $2.1 - $2.9 million, for a total cost of about $5 - $6 million.

Downstream Cost Savings/Cost Offsets

In calendar year 2004, the government of Ontario spent $25.1 million, or $915 per person, on prescription medications to treat PD, mainly L-dopa (Ontario Drugs Program Branch, Ministry of Health and Long-Term Care). We would expect, based on previous studies, that these patients would consume postoperatively about 50% of the L-dopa ($460) they consumed preoperatively, a number that is far lower than the savings documented in the literature (more than $2,000 annually) (41) Assuming 75% of people in Ontario with PD are covered by the provincial government for prescription drugs, the savings to the government would be about $343 ($915 x 50% x 75%) per person annually. A 10-year stream of savings discounted to the present at 5%, which is the discount rate recommended by the Canadian Coordinating Office for Health Technology Assessment, would therefore be $2,800 per person or about $160,000 for the current volume of 57 procedures done annually.

Because L-dopa is prescribed specifically for PD, it is the only one of the conditions for which drug-cost offsets can be readily calculated. It is important to note, however, that there are also likely large drug cost offsets associated with DBS used to treat essential tremor and primary dystonia, because reductions in drug utilization would be expected in these populations as well (Personal communication with clinical expert, February 2005). There also may be offsets from reductions in institutionalization rates in long-term care facilities for people with late-stage PD, which can cost upward of $40,000 annually.

Evidence on Costs and Cost-Effectiveness

There is a lack of published literature measuring the cost-effectiveness of DBS compared with ablative surgery or even the mean cost-effectiveness of the intervention itself. The MSAC (19) in Australia, who published a report on DBS in 2001, found that the cost of DBS is between $17,830 AU and $51,385 AU more than current ablative techniques – a range within the figures $24,420 - $28,420 calculated in the Ontario-based economic analysis. It is important to note that at the time of the MSAC report, long-term incremental effectiveness of DBS still required further study to determine a reasonable estimate of cost-effectiveness.

Because more information is now available as documented in this assessment, data from the Ontario-based economic analysis is combined with recently published literature on effectiveness. (20) The costs, including predicted offsets, per patient in the first year after surgery would be less than $25,620 ($11,597 for hospitalization + $10,000-$14,000 for device costs + $2,823 for OHIP minus $2,800 in drug offsets), a figure that is likely an overestimate due to larger expected offsets. The motor function score improved by

an average of about 22 points ($P < 0.01$) in patients with PD, regardless if DBS was first switched on or off when comparison measurements were taken. (20) Using a 10-point improvement in motor function score as a clinically significant change, one possible calculation of the cost-effectiveness of DBS to treat patients with PD would be less than $11,650 per 10-point improvement in motor function score ([$25,620 / 22 points] x 10 points).[4]

Disclaimer: This economic analysis represents an estimate only, based on assumptions and costing methodologies that have been explicitly stated. These estimates will change if different assumptions and costing methodologies are applied for the purpose of developing implementation plans for the technology.

Existing Guidelines for Use of Deep Brain Stimulation

The Medical Advisory Secretariat did not find guidelines specific to DBS. Nevertheless, guidance from the health technology assessment for Parkinson's disease by NICE (16) specified the following:

- Current evidence on the safety and effectiveness of DBS for PD appears adequate, provided normal arrangements are in place for consent, audit, and clinical governance.
- The clinical effectiveness and cost-effectiveness of DBS for PD is being evaluated by the PDSurg trail, with randomization to be completed by 2005 to 2006. Results likely will provide evidence on the appropriate use of the procedure, and physicians are encouraged to enroll patients in this trial.
- It is recommended that patients be selected with the involvement of a multidisciplinary team and that they be offered the procedure only when their disease has become refractory to the best medical treatment.

[4] A recent German study found a cost-effectiveness ratio of 920 Euros per 1-point decrease in the Unified Parkinson's disease Rating Scale. (42)

Conclusions

Policy Considerations

- According to the estimates of prevalence and evidence of effectiveness, there is a shortfall in the numbers of DBS currently done in Ontario for drug-resistant PD, essential tremor, and primary dystonia.
- Since complication rates are lower if DBS is performed in specialized centres, the number of sites should be limited.
- The cost per procedure to institutions with the expertise to undertake DBS and the human resource considerations are likely to be limiting factors in the further diffusion of DBS.

Appendix

Appendix 1

ICD-10 diagnostic codes

Parkinson's disease (ICD-10 Code: G20);
Tremor or essential tremor (ICD-10 Codes: G25.0, G25.1, G25.2);
Multiple sclerosis (ICD-10 Code: G35);
Dystonia (ICD-10 Codes: G24.0 to G24.9);
Cerebral palsy (ICD-10 Codes: G80.0, G80.3, G80.4).

CCI procedure codes

1.AE.53.^^	Implantation of internal device, thalamus and basal ganglia
Includes:	Implantation, electrodes, thalamus (e.g., for interictal measurement of epileptic discharges or stimulation of paresthesia to suppress pain)
	Implantation, semipermeable catheter, thalamus (for continuous chemical therapy)
Code Also:	Any concomitant creation of subcutaneous pocket for transmitter device (see 1.YY.84.^^)
	Any intraoperative stereotactic computer guidance (see 3.AN.94.^^)

1.AE.53.SE-JA of electrodes (e.g., recording, stimulating) using burr hole approach
1.AE.53.SZ-FT of semipermeable catheter (e.g., for continuous chemical therapy)
1.AE.53.SZ-JA of electrodes [e.g. recording, stimulating] using open approach

1.AN.53 series, with 1.AN.53.SE-JA specific to a burr hole approach (as opposed to a craniotomy).

Glossary

Activities of daily living (ADL)	Tasks that people generally do as part of a daily routine, like dressing, bathing, eating, being social, and similar activities
Akinesia	The absence or loss of control of voluntary muscle movement
Apoptosis	**Programmed cell death**
Bilateral	Having or affecting two sides
Bradykinesia	A gradual loss of spontaneous movement; an abnormal slowness of voluntary movement
Confidence interval (CI)	A range of numerical expressions within which one can be confident that the true population value the study is intended to estimate lies; usually reported as a 95% CI
Deep brain stimulation	A surgical procedure that uses electrical stimulation to deliver pulses to the brain; used to treat Parkinson's disease and other movement disorders, like dystonia and essential tremor
Dyskinesia	Abnormal neuromuscular condition characterized by disordered, impaired or excessive movement
Dystonia	A neurologic movement disorder characterized by sustained muscle contractions, causing repetitive, involuntary, twisting or writhing movements and unusual posturing or positioning
Essential tremor	A common, progressive neurologic movement disorder characterized by involuntary, rhythmic, trembling or quivering movements (i.e., tremor) of a body part
Globus pallidus	A part of the basal ganglia deep within the brain. Specialized groups of nerve cells in the globus pallidus act as a relay system to process and transmit information from the basal ganglia via the thalamus to parts of the brain that regulate motor functions (e.g., motor cortex)
Levodopa (L-dopa)	Used to treat Parkinson's disease and other neurological movement disorders, like dystonia and essential tremor
Multiple sclerosis (MS)	A progressive disease of the central nervous system characterized by destruction of myelin (demyelination), the fatty substance that protects certain long nerve fibers (axons); MS is marked by patches of hardened tissue in the brain or the spinal cord and is associated with muscle weakness, partial or complete paralysis,

	jerking muscle tremor, and tingling, and other symptoms
Parkinson's disease	A slowly progressive disease characterized by masklike facies, resting tremor, slowing of voluntary movements, festinating gait, peculiar posture, and muscle weakness, sometimes with excessive sweating and feelings of heat
Parkinsonism	A group of neurological disorders characterized by hypokinesia, tremor, and muscular rigidity
Prevalence	Total number of people with the disease at any one time
Primary dystonia	Dystonia (defined above) that is idiopathic or genetically determined
Quality adjusted life year (QALY)	A calculation created to measure the quantity and quality of life combined; it provides an indication of the benefits gained from a given therapy, treatment or technology in terms of quality of life and survival for the patient
Subthalamic nucleus	An oval mass of gray matter located beneath the thalamus
Unilateral	Having or affecting one side

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