PRE-ASSESSMENT

Deep Brain Stimulation for Patients with Parkinson’s Disease

Before CCOHTA decides to undertake a health technology assessment, a pre-assessment of the literature is performed. Pre-assessments are based on a limited literature search; they are not extensive, systematic reviews of the literature. They are provided here as a quick guide to important, current assessment information on this topic. Readers are cautioned that the pre-assessments have not been externally peer reviewed.

Introduction

Parkinson's disease (PD) is a chronic, progressive disorder of motor function. The primary symptoms of PD include bradykinesia, rigidity, tremor and postural instability. The majority of the cases suffer from idiopathic PD, where the cause of the disease is unknown. In a small number of cases, PD syndromes are associated with viral encephalitis, neurotoxins and neuroleptic drugs.

The symptoms of PD are caused by a loss of nerve cells in the pigmented substantia nigra pars compacta and the locus coeruleus of the midbrain, due to some unknown cause. Pars compacta neurons of the substantia nigra provide dopaminergic input to the striatum, which is part of basal ganglia. In PD, the loss of pars compacta neurons leads to striatal dopamine depletion and ultimately to reduced thalamic excitation of the motor cortex.

PD account for approximately 2.6% of all neurological diagnosis. The prevalence of PD is about 300 cases per 100,000 population and the incidence is estimated at 20.5 cases per 100,000 people annually. Men and women are affected equally. The age at onset of PD is variable, usually between 50 and 80 years. The mean age of onset in Canada is estimated at 52 years. Signs of PD are common in the elderly; at present one percent of the population over the age of 65 suffers from PD in America. Although the progression of disease is highly variable, the symptoms of PD may progress over time such that within 10 to 20 years total immobility can result despite drug treatment.

Currently, treatment of PD is limited to controlling the symptoms rather than preventing further neuronal degeneration. Various drugs are used, alone or in combination, to treat Parkinson's. These include dopaminergic agents (dopamine agonists, amantadine), levodopa combined with a dopa-decarboxylase inhibitor (DDC) and/or COMT inhibitors, the monoamine oxidase type B inhibitor selegiline, and anticholinergic agents. Patients with end stage disease are severely incapacitated and do not respond well to drug therapy. Surgery has played a role in the management of PD, particularly in patients who cannot achieve a satisfactory response to available medications.

There are currently three brain regions being considered as targets for functional neurosurgery for PD (other than transplantation). They are the ventral intermediate nucleus of the thalamus, the internal segment of the globus pallidus and the subthalamic nucleus. There are two options available for functional surgery at these sites: CNS lesions at these sites and deep brain stimulation.
Prior to the introduction of levodopa, PD was primarily treated by producing lesions in the thalamus (thalamotomy) or internal segment of the globus pallidus (pallidotomy) or in the subthalamic nucleus. The major disadvantage of surgical lesions is that they are irreversible and may limit the effectiveness of new procedures as they become available.

Deep brain stimulation (DBS) is a new neurosurgical procedure indicated as an adjunct treatment of the severe Parkinsonian tremors not adequately controlled by medication. DBS is a method that uses an electrode implanted into the brain with a lead connected to a subcutaneously implanted pacemaker. This permits delivery of high frequency stimulation to the desired target. Its advantages include: (1) no need to create irreversible brain lesions, (2) the possibility of low risk bilateral procedures, and (3) flexibility for altering the target site and program stimulation parameters.

On January 14, 2002, the FDA in the US approved implantable multi-programmable quadripolar DBS systems for stimulation of sub-thalamic nucleus and globus pallidus, for the treatment of PD in patients who are not adequately controlled by medication and where the tremor constitutes a significant disability. This system has also been approved in Canada (personal communication with Kathleen Savage, Health Canada).

**Research Questions**

This study was proposed to evaluate the safety and efficacy of deep brain stimulation using a systematic review approach. The following research questions can be posed:

1. Is DBS, with or without anti-Parkinsonian drugs, more effective than drug treatment alone in controlling the symptoms of PD in patients with advanced disease or patients not adequately responding to drug therapy?

2. Is DBS, with or without anti-Parkinsonian drugs, safer than drug treatment alone?

**Assessment Process**

Two PubMed searches were undertaken from 1966 to date. The Medical Subject Headings (MeSH) appropriate to the topic, such as "Parkinson Disease", were combined with appropriate treatment terms, such as "Electric Stimulation Therapy" or text phrases, such as "deep brain stimulation". Two separate study design filters were applied. One included all clinical trials, whereas the other study design filter limited the results to randomized controlled trials, systematic reviews, etc. The first strategy yielded 98 references, and the latter, 21. A search was also performed on the Cochrane Library databases, 2002, Issue no. 3.

Due to time constraints, gray literature searching was selective. The websites of specific health technology assessment (HTA) agencies and near-HTA agencies were searched and
Summary of Findings

In addition to different primary studies, we found three recently published evidence-based reviews of the clinical studies related to DBS in patients with PD. Primary studies up to December 2000 are included in two reviews. Summaries of the findings of these systematic reviews, along with limitation, are as follows:

Review I:
Davis and a co-worker from the US published a technology assessment report on DBS for essential tremors and Parkinson's disease in the year 2000. The detailed methodology and search strategy are not available in the report and the authors have not provided study selection criteria. Results of the DBS of thalamus (specifically nucleus ventralis intermedius) in patients with PD are based on data form 243 patients in five studies (case series). Complete reduction in tremors was achieved in 58 to 92% of the patients in the included studies. Major complications are rare; however, few studies presented long-term data (>12 months). Results of the stimulation of subthalamic nucleus in patients with PD were based on data from case series. There is an average improvement of 54% in motor scores and a 30 to 66% improvement in activity of daily living scores. Tremor was reduced by approximately 80% in one study of 15 patients. Results of the stimulation of internal globus pallidus in patients with PD are based on the data from five case series. Improvement in overall motor performance was observed in 30 to 80% of the patients. Complications associated with the procedure are mild and often transient. Although follow-up data beyond 12 months were limited, the available data indicate that benefits were maintained. Surgical risks associated with DBS included subdural hematomas and hemorrhaging. Based on data from 413 patients, there were 10 surgical complications (2.4%).

Review II:
In January 2002, the Medical Services Advisory Committee (MSAC) of Australia published a second report on the use of DBS for symptoms of PD. This report is a detailed technology evaluation with a well-defined search strategy and study inclusion and exclusion criteria. In this report, literature was searched from January 1966 to September 2000. The summary results of the report are as follows:

Some studies have demonstrated the added effect of DBS (thalamic, subthalamic and pallidal) over medical therapy. However, any conclusions regarding the effectiveness of DBS over medical therapy cannot be determined because of major methodological problems and poor quality of reporting in different studies. More randomized controlled studies which look at long-term effectiveness and take full account of patients' quality of life are required in order to make a valid assessment of effectiveness.
In terms of safety, limited information suggests adverse effects from DBS are generally mild, reversible and less frequent (often improving when the level of stimulation is reduced) compared to those of ablative surgery (the hallmark being permanence and irreversibility). However, particular adverse effects differed according to target site and no quantitative data are available on incidence.

Adverse effects linked with DBS include 1) those associated with the surgical procedure such as lead dislodgement and hematoma, 2) those affecting functional status such as dysarthria and transient paraesthesia, and 3) those affecting cognitive or behavioural function such as confusion and disorientation. Although a number of adverse effects have been reported, estimates of incidence are uncertain since many of the papers reviewed here did not quantify the number of patients experiencing particular effects.

Review III:
The third review on surgical treatment for PD was recently published (2002). In this review, terms used in the search strategy were reported without providing any details of the search period. However, in the bibliography, studies up to the year 2000 are included. In the review, studies are divided into three categories:

Level I: All randomized controlled studies with no sample size restriction.

Level II and III: Definition of level II and III is not provided in the review. However, the authors have mentioned that only the studies with a sample size of 20 patients or more were included.

For pallidal and thalamic stimulation, the authors concluded the evidence supporting the use of these procedures for treating Parkinsonian and motor complications remains limited. These procedures were only studied in patients with advanced disease and those with motor complications showing inadequate response to medical management.

Conclusion
Three recently published systematic reviews are available on DBS for PD patients. One of the reviews published by the MSAC of Australia in 2001 is of good quality and answers the questions posed in this pre-assessment. However, the other two systematic reviews are not transparent in terms of methodology. With our search, we could not identify a major development in the area of DBS in PD patients, which would substantially augment the conclusions of Australian MSAC review.

Based on the recent publication and quality of the Australian MSAC review, a systematic review by CCOHTA would be redundant at this time.
References


