TITLE: Deep Brain Stimulation for Parkinson’s Disease and Neurological Movement Disorders: A Review of the Clinical and Cost-Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES:

Deep brain stimulation (DBS) for the management of Parkinson’s disease and other movement disorders is a non-ablative surgical treatment that modifies the irregular neuronal activity of the target region of the brain via high frequency electrical stimulation. DBS is a life-long therapy, requiring life-long maintenance and follow-up. The procedure involves the placement of electrical leads into one (unilateral) or both (bilateral) sides of the basal ganglia of the brain. The primary target for DBS is the subthalamic nucleus (STN), although the globus pallidus internus (GPI) and the thalamus are also targets. Symptoms such as tremor or dyskinesias determine which part of the brain should be targeted.

The DBS procedure is generally performed in two separate steps: implantation of the leads (usually using stereotactic methods) followed by implantation of the electrical pulse generator to which the leads are connected. The implantable pulse generator (IPG) is implanted below the clavicle and it delivers the electrical pulses to the brain nuclei much like a pacemaker provides electrical stimulation to the heart to control heart rate. Electrical impulses are generated by a battery, which needs to be replaced at intervals of two to five years, depending on the energy levels required to control patients’ symptoms. It is usually replaced in an outpatient procedure. Newer models of IPGs use rechargeable batteries with a wearable recharging system that attaches to the IPG. Rechargeable IPG systems may not need to be surgically replaced for up to nine years.

This report will review the comparative evidence for the use of rechargeable versus non-rechargeable DBS systems, as well as describe current evidence-based guidelines for the use of DBS in the management of Parkinson’s disease and neurological movement disorders.
RESEARCH QUESTIONS:

1. What is the clinical effectiveness of rechargeable versus non-rechargeable deep brain stimulation devices for patients with Parkinson’s disease or neurological movement disorders?

2. What is the cost-effectiveness of rechargeable versus non-rechargeable deep brain stimulation devices for patients with Parkinson’s disease or neurological movement disorders?

3. What are the evidence-based guidelines for the use of deep brain stimulation devices for patients with Parkinson’s disease or neurological movement disorders?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 5, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and May 26, 2010. No filters were applied to limit the retrieval by study type for questions 1 and 2. Filters were applied to limit the retrieval to guidelines for question 3.

SUMMARY OF FINDINGS:

The search did not identify any literature comparing the clinical and cost-effectiveness of rechargeable versus non-rechargeable DBS devices. The search identified six evidence-based practice guidelines.6-11

Guidelines and recommendations

Four of the guidelines focused on Parkinson’s disease9-9 and two focused on therapies for non-Parkinson’s disorders (dystonia and essential tremor).10,11 Overall, the guidelines used robust methods to search and evaluate the literature. The objectives and patient population were specified in all the guidelines, and four of the six guidelines described the methods of their review and the level of evidence scheme used to make their recommendations. None of the guidelines restricted the literature search to a specific study type (for example, only systematic reviews). Two guidelines clearly stated the reviews upon which recommendations were made underwent external peer review. All of the guidelines agreed that the quantity and quality of studies on DBS in movement disorders is low.

In general, compared with other surgical treatments, DBS offers advantages: it is adjustable and can be tailored to the patient’s needs; it is reversible should the patient desire or need to have the system removed; and it is non-destructive.6-10

For Parkinson’s disease, the benefits of DBS include improved motor fluctuations (reduction in “off” severity and increase in “on” time), reduction in dyskinesia, suppression of medication-refractory tremor, reduced medication use, improved performance in activities of daily living, and
improved quality of life. The American Academy of Neurology (AAN) concluded the improvement with DBS (except for increased tremor control) is equivalent to the improvement seen with medications and that the benefit persists for a longer amount of time. For the limitations of DBS, implantation is associated with the same potential risks of surgical adverse events as with similar neurosurgical procedures, including hemorrhage, stroke, seizure, headache, and infection. Additional complications specific to DBS include lead migration, device malfunction or failure, dysarthria, weight gain, depression, behavioural and cognitive problems, which are often transient and/or modifiable. DBS has not been shown to be protective by maintaining the remaining dopamine cells, nor has it been shown to slow the progression of Parkinson’s disease. Furthermore, DBS does not improve the non-motor symptoms of Parkinson’s disease, such as depression and anxiety.

Based on these findings, the guidelines recommend bilateral DBS be used for Parkinson’s patients who do not achieve adequate control of motor fluctuations and dyskinesia with optimized medical therapy, who have medication-refractory tremor, or who are intolerant of medical therapy. DBS may be used for patients with mild or well-controlled comorbidities, although these factors should be considered in a risk evaluation of the procedure. Serious cognitive, psychiatric, and medical comorbidities are relative contraindications for DBS and DBS is not recommended for patients with advanced dementia, or a limited life expectancy due to a comorbid condition. The guidelines noted there is insufficient evidence to support or refute the efficacy of DBS of the GPi or thalamic nucleus in improving smooth motor fluctuations, reducing dyskinesia, or reducing medication usage. According to the National Institute for Health and Clinical Excellence (NICE) 2006 guidelines, observational data suggest STN stimulation my lead to greater improvement in motor scores and a greater reduction in levodopa dose and depression scores compared with GPi and thalamic stimulation, whereas GPi stimulation may lead to less cognitive impairment. The operation for thalamic stimulation carries the greater risk of serious adverse events such as cerebral infarction and hemorrhage and should be reserved for severe disabling tremor and when STN cannot be performed.

For essential tremor, DBS of the motor thalamus is effective in reducing contralateral limb tremor and is recommended for treatment of limb tremor that is refractory to medical management. Bilateral thalamic DBS is recommended to suppress bilateral upper limb tremor; however, bilateral DBS is associated with more frequent adverse events than unilateral DBS. Data for the use of DBS for head tremor and voice tremor in essential tremor are limited and conflicting. DBS is at least as effective as thalamotomy in essential tremor and appears to have fewer adverse events.

For dystonia, DBS improves dystonia scale scores and global disability scores after three months of therapy and the effects persist for at least 12 months of therapy. Thus, DBS is recommended for use in patients with dystonia, although the severity of symptoms may progress over time.

**Limitations**

Overall, the guidelines used pre-specified and robust methods in their development. However, most may be considered out-of-date and require updating. Recommendations regarding the use of DBS were limited by the paucity of primary studies. Most of the guidelines were based on studies that were not randomized or blinded. None of the observational studies used a non-
surgical comparison group and they tended to have short follow-up periods (typically less than 12 months). Therefore, the effectiveness of DBS versus standard medical therapy was not considered in the development of these guidelines.6-11

Due to the date of publication, none of the guidelines included the results from a recent multi-centre, randomized, blinded, placebo-controlled trial that compared the efficacy and harms of DBS with best medical therapy for patients with advanced Parkinson’s disease and motor complications (n = 255).12 Patients who received DBS (pooled STN and GPi) gained statistically more “on-time” without troubling dyskinesia at six months compared with best medical therapy (mean difference 4.5 hours; 95% confidence interval: 3.7 to 5.4). In addition, the DBS-treated patients had statistically significantly higher rates of clinically meaningful motor improvement and improved quality of life. Thus, DBS was more effective than the best medical therapy for the management of moderate to severe Parkinson’s disease. However, the prevalence of serious adverse events was higher in the DBS group than in the best medical therapy group (40% versus 15%, respectively) and were largely related to the surgical procedure (namely infection, headache and pain). One patient died of cerebral hemorrhage.12

None of the guidelines addressed the implantation of rechargeable IPGs compared with non-rechargeable systems.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

No literature is available comparing the clinical and cost-effectiveness of rechargeable versus non-rechargeable DBS systems in the management of Parkinson’s disease and neurological movement disorders. Moreover, there is a dearth of primary studies evaluating the efficacy and safety of DBS for movement disorders for the development of practice guidelines. The clinical practice guidelines agree that the data to support the use of DBS is limited in quantity and quality. All, however, recommend the use of DBS among patients who do not achieve adequate control of motor fluctuations and dyskinesia with best medical therapy, who have medication-refractory tremor, or who are intolerant of medical therapy. The current available data suggests DBS can relieve symptoms and improve the overall functioning and quality of life of the patient. Unlike respective ablative therapy, DBS is reversible and it allows titration of stimulation parameters and may be associated with less morbidity.

Several clinical practice authorities have recommended the use of DBS in patients with advanced Parkinson’s disease and other movement disorders. The lack of information on the clinical and cost-effectiveness of rechargeable DBS systems may wish to be considered when making decisions regarding its use.

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