Centre universitaire de santé McGill
McGill University Health Centre

Technology Assessment Unit of
the McGill University Health Centre

Subthalamic Deep Brain Stimulation (DBS): Clinical efficacy, safety and cost compared to medical therapy for the treatment of Parkinson's Disease

Report Number 38

November 27, 2009

Report available at **www.mcgill.ca/tau/**

Report prepared for the Technology Assessment Unit (TAU)

of the McGill University Health Centre (MUHC)

by

Irene Pan **and** ***Nandini Dendukuri***

with the assistance of
Dr. Maurice McGregor

Approved by the Committee of the TAU on December 15, 2009

TAU Committee

Invitation.

This document was developed to assist decision-making in the McGill University Health Centre. All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.

E-mail address:

maurice.mcgregor@mcgill.ca ***nandini.dendukuri@mcgill.ca***

ACKNOWLEDGEMENTS

The expert assistance of the following individuals is gratefully acknowledged:

Dr. Abbas Sadikot, Department of Neurosurgery, MUHC
Ms. Elizabeth Coté, Department of Neurosurgery, MUHC
Mr. Nicolas Robert, Department of Finance, MUHC

Report requested on February 1, 2008 by Françoise Chagnon, Director of Professional services, MUHC

Commenced: June 1, 2008

Completed: Nov 27, 2009

Approved: December 15, 2009

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

DBS	Subthalamic nucleus Deep brain stimulation
HTA	Health technology assessment
L-dopa	Levodopa
MNH	Montreal Neurological Hospital
MNI	Montreal Neurological Institute
OR	Operating room
PD	Parkinson's disease
PDQ-39	Parkinson's disease questionnaire – 39 items
QoL	Quality of life
STN	Subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
GPi	Globus Pallidus Interna

MESSAGES

- There is good evidence that Deep Brain Stimulation of the Subthalamic Nucleus is an effective and safe treatment for patients with medically refractory Parkinson's disease
- Deep Brain stimulation is associated with significant improvement in motor function, quality of life and L-dopa dose reduction
- There is a small, but non-negligible, risk of serious adverse events such as cerebral hematoma associated with Deep Brain Stimulation
- It is important that Deep Brain Stimulation be performed by an experienced, multidisciplinary team to ensure optimal selection of patients and reduce the risk of adverse events.
- The McGill University Health Centre should support and expand the Deep Brain Stimulation program at the Montreal Neurological Hospital and Institute to the extent possible

SOMMAIRE

Contexte:

La stimulation profonde du noyau sous-thalamique (SNS) est le traitement chirurgical le plus couramment utilisé chez les patients affectés par la maladie de Parkinson et chez qui les médicaments ont peu d'effets. Une évaluation technologique publiée en 2005 par le Ministère de la santé de l'Ontario concluait que la SNS entraînait une amélioration à court terme de la motricité et une réduction de la thérapie médicamenteuse. Cependant, des interrogations persistent en regard de la performance du traitement à long terme, plus particulièrement son impact sur la qualité de vie, sur les fonctions cognitives, sur l'innocuité ainsi que son coût-efficacité. Depuis 2005, un certain nombre d'études concernant ces enjeux (comprenant 3 études randomisées et 3 études de cohortes avec un suivi important) ont été publiées. La SNS est pratiquée au CUSM depuis 22 ans et le manque de fonds est responsable de l'arrêt de ce traitement pour une période de 3 mois chaque année, ce qui se traduit par une liste d'attente de 6 mois, actuellement.

Objectifs :

L'objectif de ce rapport est de faire une revue systématique de la littérature portant sur l'efficacité clinique et l'innocuité de la SNS depuis 2005 et d'évaluer le budget requis pour répondre à la demande de ce traitement au CUSM.

Méthodologie :

L'évaluation technologique publiée en 2005 par le Ministère de la santé de l'Ontario fut revue et une recherche de la littérature fut menée pour identifier les articles pertinents publiés après ce rapport. De même, le personnel de l'Hôpital Neurologique de Montréal (HNM) fut rencontré pour connaître le nombre de patients traités annuellement au CUSM, le coût de l'appareillage ainsi que le budget manquant.

Résultats :

Impact sur la santé :

Amélioration de la motricité et de l'utilisation de la L-dopa.

Trois études randomisées comparant l'efficacité et l'innocuité de la SNS vs le traitement médical furent identifiées. Toutes ces études montrèrent que les patients traités par SNS avaient une amélioration soutenue de leurs fonctions motrices et de leurs activités quotidiennes jusqu'à 6 mois après la chirurgie et ce, uniquement sous stimulation, sans médication. De plus, il fut possible de diminuer la dose de L-dopa d'environ 50% avec la SNS. Enfin, les résultats d'études d'observation montrèrent le maintien d'une amélioration importante de la motricité suite à la SNS jusqu'à 5 ans.

.

Qualité de vie.

La qualité de vie des patients avec SNS, tel que mesurée à l'aide du questionnaire relatif à la maladie de Parkinson (PDQ-39) comprenant 39 items, s'était améliorée d'environ 20% tandis que celle des patients sous médication, seulement, demeurait inchangée ou diminuait après 6 mois.

Effets indésirables.

La SNS était associée à un taux de 2,6 - 4% d'effets indésirables permanents tel que l'hématome cérébral, et un taux de 40-50% d'effets indésirables temporaires. Certaines études sur la SNS montrèrent une détérioration de l'élocution. Une courte étude menée au CUSM chez les patients traités par SNS montra qu'il n'y avait pas de changements importants de la fonction cognitive chez les patients sans dépression ou démence. Une revue des cas de SNS effectués au CUSM depuis les quinze dernières années montra un taux de risque de 0,5% pour la présence d'un hématome intracérébral non symptomatique.et aucun cas de déficit neurologique permanent.

Enjeux financiers :

Achalandage.

De façon générale, 25 nouveaux patients sont traités par SNS au cours des 9 premiers mois de l'année (de janvier à septembre) au CUSM. Durant les 3 mois suivants, aucun traitement n'est fait dû à un budget insuffisant pour l'achat de l'appareillage. Si les traitements étaient disponibles pour tous les mois de l'année, le nombre de patients pourrait être augmenté de 15 patients par année. Au Québec, les besoins représentent environ 35 traitements additionnels par année.

Coût d'un traitement.

Au CUSM, le coût moyen d'un traitement (incluant le suivi d'une année) est environ 27 444 $ (incluant l'appareillage au coût de 16 400 $).

Déficit budgétaire.

Le budget requis pour faire l'acquisition de l'appareillage pour 15 cas supplémentaires serait de 246 000 $. L'impact budgétaire annuel (dû à l'achat de l'appareillage et à l'utilisation des ressources du CUSM) serait environ 411 672 $ pour les 5 premières années et 619 154 $ pour les 5 années suivantes.

Coût-efficacité.

Le coût d'un traitement par SNS entraînant une diminution de 10 points dans le pointage UPDRS a été évalué à 11 650 $ dans l'étude ontarienne. De plus, deux études sur le coût-efficacité ont montré une diminution significative du coût moyen de médication et de l'utilisation des ressources hospitalière par patient suivant un traitement par SNS.

Conclusion :

Il existe des évidences certaines à l'effet que le traitement par SNS améliore la fonction motrice et maintient la qualité de vie des patients chez qui la médication a peu d'effets, pour une période d'au moins 5 ans. Il est important que cette intervention soit réalisée dans un centre spécialisé tel l'HNM où l'expertise et l'expérience sont déjà présentes. Une sélection optimale des patients ainsi qu'un suivi adéquat sont nécessaires pour minimiser les risques de complications. Avec une liste d'attente qui augmente au Québec, une augmentation de l'achalandage de 15 patients par année à l'HNM exigerait un montant de 246 000 $ par année pour l'appareillage ou un budget total d'environ 411 672 $ par année (excluant les coûts reliés aux complications) pendant les 5 premières années. Il est à noter que la réduction de la prise de médicaments entraînerait des économies importantes pour le Ministère de la santé, mais n'aurait aucun impact sur le budget du CUSM.

Recommandations :

- **Le comité recommande que la stimulation profonde du noyau sous-thalamique soit une procédure qui doit être maintenue au CUSM et augmentée selon les disponibilités.**

- **Au moment de renouveler la demande de fonds nécessaires pour l'acquisition de l'appareillage pour SNS aux autorités de la santé, le CUSM pourrait mettre l'accent sur les points suivants :**
    - **Le temps d'attente pour cette procédure est important (de 6 mois à 1 an, actuellement). L'on estime qu'au Québec les besoins pour ce traitement se traduisent par environ 35 procédures additionnelles par année et que l'ajout de 15 patients par année à l'HNM exigerait un montant additionnel de 246 000 $ par année pour l'acquisition de l'appareillage, seulement.**
    - **La SNS est une procédure hautement complexe qui requiert une équipe qualifiée et expérimentée. Pour maintenir une telle équipe, un nombre important de patients est nécessaire, exigeant que cette procédure soit restreinte à quelques**

centres, seulement. Et l'Hôpital Neurologique de Montréal est un tel centre depuis 1985.

- **La pratique actuelle selon laquelle les chirurgies ont lieu durant les neuf premiers mois de l'année (jusqu'à ce que le budget soit épuisé) et redémarrent trois mois plus tard est hautement inefficace et milite contre l'atteinte des meilleurs résultats opératoires.**
- **Il existe des évidences selon lesquelles le coût des soins de santé (excluant ceux du CUSM) en regard des patients atteints de la maladie de Parkinson, pourraient diminuer d'environ 50% suite au traitement par SNS.**

EXECUTIVE SUMMARY

Background: Subthalamic nucleus deep brain stimulation (DBS) is currently the most widely used surgical treatment for medically-resistant Parkinson's disease (PD). A health technology assessment (HTA) published by the Ontario Ministry of Health in 2005 concluded that DBS was associated with short-term improvement in motor function and a reduction in medical therapy. However, questions regarding the long-term performance of the treatment, particularly its impact on quality of life, cognitive function, safety and cost-effectiveness remain. Since 2005, a number of studies addressing these issues (including 3 randomized controlled trials (RCTs) and 3 cohort studies with a longer follow-up time) have been published. DBS has been performed at the MUHC for 22 years. Currently, insufficient funding has resulted in the procedure being halted for 3 months each year, resulting in the wait time for this procedure increasing to 6-months.

Objective: To systematically review the literature on effectiveness and safety of DBS since 2005, as well as estimate the budget required to meet the shortfall at the MUHC.

Methodology: The 2005 Ontario HTA was reviewed, and a literature search was performed to identify relevant articles published after this report. We consulted with staff at the MNH to obtain estimates of the number of patients who receive this treatment annually at the MUHC, the cost of the device and the estimated shortfall.

Results:

Health Outcomes:

Improvement in motor function and L-dopa use. Three RCTs comparing efficacy and safety of DBS to medical therapy, were identified. All three studies showed that patients treated by DBS improved and maintained their improvement in motor functions and activities of daily living in the "medication-off, stimulation-on" state for up to 6 months following surgery. Furthermore, it was possible to decrease L-dopa dosage by roughly 50% with DBS. Observational study results indicated maintenance of significant motor function improvement by DBS up to five years.

Quality of life. Patient quality of life (QoL) as measured by the 39-item Parkinson's Disease Questionnaire (PDQ-39) improved by roughly 20% in DBS patients, while patients who were on medication only did not show improvements or had diminished QoL at 6 months.

Adverse events. DBS was associated with a 2.6-4% risk of permanent adverse events, such as cerebral hematoma, and a 40-50% risk of temporary adverse events. In a number of studies DBS was associated with deterioration in verbal fluency. One small study of DBS patients treated at the MUHC, concluded there were no clinically meaningful changes in cognitive function among patients without depression or dementia. A review of the DBS cases done at the MUHC over the last fifteen years showed no cases of permanent neurological deficit, and a 0.5% risk of intracerebral hematoma, which were not symptomatic.

Cost issues:

Turnover. Currently, 25 new DBS treatments are done during the first 9 months of the year (January-September) at the MUHC. During the remaining 3 months, no procedure is done due to lack of sufficient budget for the devices. If operating could be continued all year round, turnover could be increased by a further 15 patients per year. In the province of Quebec, there is an estimated need for approximately 35 additional procedures per year.

Unit cost. The average cost to the MUHC of each procedure (including one year of follow-up) is approximately $27,444. (Equipment Cost $16,400)

Budget shortfall. The budget required to purchase the devices for 15 additional cases would be $246,000. The total annual budget impact (due to device costs and MUHC resource use) would be approximately $411,672 for the first 5 years and $619,154 for the next 5 years.

Cost effectiveness. The cost of DBS per 10-point decrease in the UPDRS score has been estimated to be $11,650 in the Ontario study. Two cost-effectiveness studies have shown that there is a significant reduction in the average cost of medication and hospital resource use per patient following DBS treatment.

Conclusions: There is clear evidence that Deep Brain Stimulation improves motor function and sustains quality-of-life in patients with medically-resistant disease for a period of at least 5 years. It is important that this intervention be performed by a skilled and experienced centre such as the MNH where expertise and experience have already been accumulated. Optimal

selection and follow-up of patients is necessary to minimize the risk of adverse outcomes. There is an increasing waiting list in Quebec. To increase the turnover at the MNH by 15 patients per year would require $246,000 per year for equipment, or a total of approximately $411,672 (excluding costs of treating procedure related complications) per year during the first 5 years. Through reduction in medication costs there would be a significant saving from the point of view of the provincial health authority, but this would not affect the MUHC.

Recommendations:

- **The committee recommends that Deep Brain Stimulation of the Subthalamic Nucleus is a procedure that should be maintained and expanded at the MNH to the extent possible.**

- **At the time the MUHC renews its application to the health authorities for the necessary funds to support acquisition of DBS equipment, the following points could be stressed:**
    - **There is a significant wait time for this procedure, (currently 6 months to 1 year). It is estimated that in Quebec there is a need for approximately 35 additional procedures per year. An increase at the MNH of 15 patients per year would require an additional $246,000 per year for expandable equipment only.**
    - **DBS is a highly complicated procedure requiring a skilled and experienced team. To maintain such a team a high turnover is necessary and accordingly, the procedure should be restricted to very few centres. The MNH has been such a centre since 1985.**
    - **The current practice of operating for nine months (until the funds are expended), and then starting again three months later is highly inefficient and mitigates against achievement of the best operative results.**
    - **There is evidence that the cost to the provincial health administration (but not the MUHC) of maintaining a PD patient could decrease by approximately 50% following the procedure**

1 INTRODUCTION

1.1 Objective:

The objective of this health technology assessment (HTA) is, 1) to systematically review the literature since 2005 on efficacy and safety of bilateral subthalamic deep brain stimulation (DBS) compared to best medical therapy for the treatment of Parkinson's disease (PD), and, 2) to estimate the cost of this procedure from the point of view of the MUHC.

1.2 Parkinson's disease:

Parkinson's disease is a chronic, progressive neurodegenerative disorder characterized by symptoms of tremor, rigidity, slow movements, and poor balance.[1] As the symptoms worsen, the patient suffers troubled sleeping, slurred speech, difficulty swallowing and impaired vision. Eventually, quality of life (QoL) is greatly diminished, and patients are incapable of independent living.

1.3 Treatment for PD:

1.3.1 Levodopa

The current gold standard medical treatment for PD is oral administration of levodopa (L-dopa), a precursor of dopamine that can cross the blood-brain barrier to increase dopamine levels in the brain. Despite effective control of PD symptoms by L-dopa, prolonged use results in motor function fluctuations and dyskinesia.[2] In some patients Levodopa-induced dyskinesia may be more disabling than the motor impairment caused by PD itself. The present report focuses on comparing two kinds of PD therapy, medical and subthalamic deep brain stimulation among such patients.

1.3.2 Deep brain stimulation

Deep brain stimulation (DBS) involves the administration of electrical impulses to the targeted brain area through a surgically implanted neurostimulator. The subthalamic nucleus (STN) is currently the most common target of DBS for PD, and the focus of this review. The ventral

intermediate nucleus of the thalamus (Vim) and globus pallidus interna (GPi) have also been considered as targets.

Selection for DBS: Over time, approximately 10-15% of Parkinson's disease patients fail to respond to an increase in L-dopa dose and are considered suitable candidates for receiving DBS. Patients are required to go through a standardized dopamine challenge, during which they receive increasingly higher doses of dopamine to test whether this affects their reaction. Patients who fail to react are considered suitable candidates for DBS.[3] A major goal of DBS is to reduce L-dopa dosage.

Surgery: The DBS apparatus consists of three components: the lead (an electrode), the extension, and the neurostimulator (that contains the battery). All three parts are implanted under the skin, with the electrode placed in the brain, the neurostimulator implanted in the lower chest or upper abdomen, and the extension connecting the two devices (Figure 1).

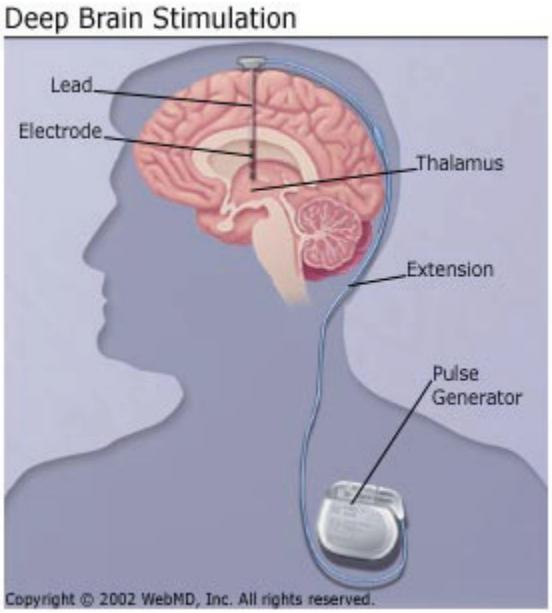

Figure 1: Deep Brain Stimulation

Surgery is carried out in two stages. The first involves implantation and positioning of the electrode. Before inserting the electrode, the neurosurgeon maps the brain using magnetic resonance imaging (MRI) to locate the target area. The electrode, a thin insulated wire, is the

only hardware directly implanted into the brain. It is inserted through a small opening in the skull and its tip is positioned within the target area. The second stage of the surgery involves implantation of the neurostimulator (generator) in the chest, and sub-cutaneous implantation of the extension from the head to the stimulator.

2 METHODS

2.1 Literature update since 2005

A health technology assessment report published in 2005 by the Ontario Health Ministry provided a systematic review of the literature on the efficacy of DBS as well as an estimate of its cost-effectiveness. To update this report, we carried out a literature search for relevant articles published since 2005. We were particularly interested in RCTs of DBS vs. medical therapy, studies with a long-term follow-up, articles reporting on the impact of DBS on QoL and adverse events associated with the DBS procedure. Appendix 1 contains the list of databases searched, keywords used and the article selection strategy. Given the paucity of the literature, both randomized controlled trials (RCTs) and observational studies were included and critically evaluated. We also searched for articles based on DBS patients treated at the MUHC.

From the selected studies we extracted results related to the impact of DBS on motor function, activities of daily living, L-dopa use, quality of life and adverse events. The severity of PD is measured using the Hoen-Yahr Staging of Parkinson's Disease.[4] Motor function is typically assessed with the Unified Parkinson's Disease Rating Scale (UPDRS),[5] while QoL is assessed with the Parkinson's Disease Questionnaire (PDQ-39).[6] More details on these validated scales appear in Appendix 2.

2.2 Quality assessment

Quality assessment for RCTs was carried out using the Jadad scale.[7] The Jadad scale scores from 0 (low) to 5 (high). Since double-blinding is not possible in studies of DBS, the maximum achievable score is 3 (2 for appropriate description of the methods for randomization and 1 for appropriate description of withdrawals and dropouts).

3 RESULTS

3.1 Summary of the 2005 Ontario Health Ministry report:

3.1.1 Review of individual studies

In 2005, an Ontario Health Ministry report[8] reviewed two RCTs and 12 observational studies evaluating DBS. The two RCTs showed a significant beneficial effect of DBS on motor function during a 24-hour period in the medication-off condition. The medication-off condition, i.e. when the patient is not using any L-dopa, represents the worst case situation when the patient receives no benefit from L-dopa. Both RCTs and observational studies reported on the change in motor function and L-dopa use at follow-up compared to baseline. Follow-up ranged from 6-months to 5-years. In general, DBS was associated with a statistically significant improvement in motor function, ranging from 22% to 71% when the patient was in the 'medication off' condition. The improvement in the 'medication on' condition, when the patient is receiving the maximal benefit of L-dopa, was smaller, ranging from 0% to 54%. DBS was associated with a roughly 50% decrease in post-operative L-dopa use. Permanent adverse events related to the DBS device or procedure included intracerebral hemorrhage (3%-5%), dementia (4%), pulmonary embolism (1%) and paralysis (1%)

3.1.2 Cost-effectiveness analysis

The total cost per case, including one-year follow-up, for DBS surgery was estimated between $24,420 and $28,420 (hospitalization: $11,597 + device cost: $10,000-14,000 + professional fees: $2,823 – reduction in drug intake: $2,800). Based on these cost estimates and an estimated average decrease (improvement) in the UPDRS motor function score of 22 points (or 20%) in the first year after surgery, the cost-effectiveness of DBS for a 10-point decrease UPDRS motor subscale was estimated to be $11,650. They estimated that while roughly 1850 people are eligible only 60 surgeries are performed annually in Ontario.

3.1.3 Conclusion

The report concluded that there was reliable evidence that DBS controls advanced symptoms of Parkinson's disease during the 1st year after the intervention, but less reliable evidence of this benefit lasting for a longer term. The report also concluded that since complication rates are

lower when DBS is performed in specialized centres, the number of sites should be limited. Finally, it suggested that 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.

3.2 Results of post-2005 literature search

A flow chart summarizing the literature search and study selection can be found in Figure 2. We found results from three RCTs comparing DBS to medical therapy (Table 1).[9-12] In addition, we also extracted data from the intervention arm of five RCTs comparing DBS to other interventions besides medical therapy (Table 2).[13-18] We also identified one RCT by Wojtecki et al.[19] that studied the efficacy and safety of high vs. low frequency DBS to investigate its effect on verbal fluency.

Due to heterogeneity of study populations and methods of reporting we decided not to carry out a meta-analysis. All RCTs had short follow-up periods (6-18 months). However, we identified 3 observational studies of the long-term effects of DBS that had a follow-up from six months to five years.[20, 21] Another six observational studies[22-27] reporting on QoL and mortality rate in more detail and two cost-effectiveness studies[28, 29] were retained.

We also retained 2 studies based on patients at the MUHC.[30, 31] The objective of these studies was to evaluate the impact of DBS on cognitive function, communication and mood.

3.3 Effect of DBS on health outcomes

3.3.1 L-dopa dose and motor function

Results from RCTs:

In four studies, the average reduction in L-dopa dose at 6 months post-DBS ranged from 50-71%[9-11, 16] (Tables 1 and 2). An average reduction of 33-73% in L-dopa dose was maintained at 12 months after surgery.[10, 13, 15, 16] Levodopa-induced complications (UPDRS IV) were also reduced by 83% and 70.5% at 6- and 12-month after surgery in DBS patients compared to patients on medical therapy.[10, 16] In patients who received only medication for PD therapy, L-dopa dosage decreased only slightly[9, 12] or even increased over time (Table 1).[10, 11]

DBS patients' ability to perform activities of daily living (ADL) (as measured by UPDRS II) was significantly improved[9, 15, 16] at 6 and 12 months after surgery, whereas medical therapy patients experienced no improvement.[9]

At 6 month follow-up, motor function (UPDRS III) measured during "stimulation-on, medication-off" improved by approximately 22.5 points (on a 56-point scale)[9, 15, 16] or approximately 50%[10] compared to 0.4 points in medical therapy patients.[9] At 12 months, similar results were obtained.[13, 15, 16] Patients treated with medication only showed a minimal change[9, 16] or a worsening[10] during the same time.

Results from observational studies:

Wider et al.[21] followed 50 DBS patients and reported data on 37 at their five-year follow-up. Improvement in motor function measured during the "stimulation-on, medication-on" phase was maintained from six months to five years post-surgery. L-dopa dosage reduction was 83%, 65%, and 57% at 6-month, 1-year, and 5-year post-surgery, respectively. The authors[21] observed significant and steady increases in voltage for stimulation with stable frequency (Hz).

3.3.2 Quality of life as measured by the PDQ-39

Results from RCTs:

DBS was associated with an improvement in patient QoL (PDQ-39) of 17%-24% up to 6 months post-operatively in 2 RCTs[9, 11] and up to 18 months post-operatively in 1 RCT[30], compared to no improvement in the medical therapy group (Table 4). Two of the RCTs reported that while there was significant improvement on the mobility, stigma, bodily discomfort and activities of daily living subscales at 6-month follow-up, there was only minimal improvement on the social support, cognition and communication sub-scales[9, 11].

Results from observational studies:

Similar results were also reported in 3 observational studies with a 12 month follow-up - 2 cohort studies[22, 23] and 1 study comparing DBS patients to matched medical therapy controls[25],

leading one of the studies to conclude that benefits of DBS were limited to the physical aspects of quality of life[19]. Two of the observational studies found that, DBS patients had worse communication at 12-months [23,25], however unusual results in one study and the unadjusted analysis in the other make them difficult to interpret. In the study by Erola et al., the finding of worse communication was coupled with no significant improvement in mobility, which is unusual[23]. In the study by Montel et al., results were not adjusted for baseline differences in communication[25].

Two studies evaluated patients' perception of their change in quality of life following DBS. Both studies found that patients' subjective perception of improvement in QOL was lower compared to objectively measured improvement in QOL[25,26]. Gronchi-Perrin et al.[26] found that, on average, patients perceived their post-operative ability to communicate to have worsened and their performance on activities of daily living to have remained unchanged.

To assess the long-term improvement in patients' QoL, Siderowf et al.[20] followed 18 patients for an average of 35.9 months (range 18-57 months). Although patients' social function, ability to communicate, and cognition deteriorated, all other subscales showed significant improvement.

3.3.3 Neurocognitive function

3.3.3.1 Verbal fluency

Results from RCTs:

Both semantic[12] and phonemic[13, 11, 12] fluency deteriorated with either medical therapy or DBS treatment, but medical therapy patients still performed significantly better than DBS patients on the verbal fluency tasks.

Wojtecki et al.[19] further investigated the hypothesis that stimulation frequency is associated with declined verbal fluency post-DBS. Verbal fluency was significantly better when DBS was administered at low frequency (10Hz compared to 130Hz); however, motor function was significantly better with a high frequency stimulation setting.

Results from observational studies:

Fraraccio et al.[9] studied changes on several tests of cognitive function (including verbal memory and language) among 15 DBS patients treated at the MUHC. The time since DBS treatment ranged from 4-49 months. Only patients without dementia or major depression were included in this study. The authors concluded that neurostimulation does not cause a "clinically meaningful" decline in cognitive function in well-selected PD patients with no history of dementia or depression.

3.3.3.2 Depression and anxiety

Results from RCTs:

Neither DBS nor medical therapy was associated with a change in depression scores during the 6-month follow-up period in RCTs.[9, 11] One RCT, among patients with less severe PD, found an improvement in mood as assessed by the Montgomery-Asberg Depression Rating Scale and a significant decrease in anxiety as measured by the Brief Anxiety Scale up to 18 months post-DBS.[10] In comparison, changes in the medical therapy group were insignificant.

Results from observational studies:

Berney et al.[30] studied mood stability in 15 consecutive patients treated at the MUHC. Patients had DBS at least 1 year prior to recruitment. The authors concluded that DBS does not induce any clinically relevant mood instability assessed by the Profile of Mood State (POMS), which encompasses three major subcategories: depression, anxiety, and hostility.[30]

3.4 Risk of adverse events following DBS

Results from RCTs:

Table 3 summarizes the complications and adverse events in DBS patients reported by RCTs that included a DBS arm. We separated adverse events into 4 groups depending on whether they resulted in death, disability, morbidity or discomfort. It was difficult to pool results because of the non-uniform method of reporting across studies.

Two RCTs reported differing information on the total risk of temporary adverse events. While Deuschl et al.[9] found a lower risk in DBS patients (50% of DBS vs. 64.1% of medical therapy patients had at least one temporary adverse event (p=0.08)), Weaver et al.[11] found a higher risk (40% of combined Gpi/DBS patients vs. 11% of medical therapy patients had at least one incidence of a serious adverse event(p<0.01[a])).

According to the definition used by Weaver et al.[11] serious adverse events included surgical site infection, nervous system disorders, psychiatric disorders, device-related complications such as lead repositioning and cardiac disorders. Moderate adverse events included falls, gait disturbance, depression and dystonia. The majority of the adverse events were resolved by the end of the follow-up period.[9, 14]

The most common cause of procedure-related death was intracerebral hematoma, the risk of which was reported to range 2.6%-4.0% (Table 3).[9, 15, 16, 18]

Results from observational studies:

Voon et al.[27] estimated that the first year suicide rate in PD patients post-DBS was 263/100,000 persons/year, which was significantly higher than the highest expected, age-, gender-, and country-adjusted suicide rates posted by the World Health Organization (Standardized Mortality Ratio: 12.63 (95% CI: 8.12, 19.65)). The suicide rate remained heightened up to four years after the start of DBS (Standardized Mortality Ratio: 1.81 (1.07, 3.08)). The authors mention that this is disconcerting given that earlier studies of suicide among Parkinson's disease patients did not find an increased risk compared to the general population. However, the study by Voon et al.[27] did not compare suicide rates between DBS patients and patients with medically-refractory Parkinson's disease.

The authors[27] also identified the following risk factors for suicide among DBS recipients: younger age (either at the time of DBS treatment or onset of PD), single marital status, more severe post-operative depression and apathy, previous suicide attempt or impulse control disorder, and larger percent decrease in L-dopa dose. They recommended that patients should

[a] Estimated based on data reported in the article.

undergo a multi-disciplinary assessment and follow-up post-DBS. Another retrospective cohort study identified dementia as the only significant prognostic factor in mortality post-DBS.[26]

3.5 Cost effectiveness of DBS

Results from observational studies:

A prospective cohort study in Spain[29] compared 14 DBS patients to 15 patients on medical therapy. They found that DBS cost €7,601 more than medical therapy at 12 months. This study found that despite the need for adjustment of stimulation and medication, DBS patients made fewer outpatient visits during the follow-up period than medical therapy patients. Though the pharmacological costs were similar in both groups at baseline, the cumulative costs in the medical therapy group were roughly double that in the DBS group (median cost in the DBS group: €3,132; median cost in the medical therapy group: €5,950). The mean gain in quality-adjusted life years (QALYs) was 0.76±0.03 for DBS treatment and 0.54±0.06 for medical therapy. The incremental cost-effectiveness ratio per QALY (ICER/QALY) of DBS compared to medical therapy was €34,389.

Meissner et al.[28] studied the health care utilization and pharmacological costs of 46 DBS patients over a 3-year period. They found a significant decrease in total health care expenses (€7,223±717 in the second year post-DBS compared to €15,991±2636 in the year prior to DBS). They estimated that the incremental cost per unit increase in the UPDRS III was €979, 12 months after surgery, a figure which is comparable to the Ontario estimate of $1,165.[8]

4 CONCLUSIONS FROM SYSTEMATIC REVIEW

A systematic review of the literature since 2005, shows that the promising effect of DBS in improving motor skills and reducing L-dopa use has now been confirmed by RCTs. Further, these studies have shown that these beneficial effects are accompanied by significant improvement in QoL during the first 18 months after treatment. Based on observational studies, the benefits may last for at least five years, (the duration of the longest follow-up).

Though most studies have concluded that DBS is a safe procedure, risk of temporary procedure-related complications is significant, and the risk of permanent procedure-related

complications is not negligible. Some studies have also found a small negative effect of DBS on some aspects of cognitive function and verbal fluency. The clinical significance of these effects remains to be explored. A small study by the centre at the MNH concluded that by selecting patients carefully such negative effects can be avoided. In the absence of information from RCTs with a longer duration of follow-up, expert centres such as the MNH could provide valuable observational data on the frequency and clinical significance of adverse outcomes following DBS.

The concerns mentioned above and the high cost of the procedure underline the importance of concentrating DBS at a limited number of centers of expertise, such as the MUHC, in order to reduce the risk of adverse events and to improve outcomes.

5 DEEP BRAIN STIMULATION AT THE MUHC

5.1.1 History and patient profile

Deep brain stimulation has been carried out at the Montreal Neurological Hospital and Institute since 1987 as part of a multidisciplinary supra-hospital program which harnesses specialized resources at the MNH and brings together specialists throughout Quebec. Dr. Abbas Sadikot has been involved in carrying out these procedures since 1993. The multidisciplinary team at the MNH includes Dr. Sadikot himself, Dr. Michel Panisset (neurologist) who is located at Hôpital Notre Dame and is an associate neurologist at the MUHC, 4 other specialized neurologists at Notre Dame (Dr. Solange, Dr. Chouinard, Dr. Blanchet, Dr. Jodoin), 4 specialized neurologists at the MUHC (Dr. Dagher, Dr. Lafontaine, Dr. Fon, Dr. Aube, Dr. Postuma), 2 neuropyschologists (Dr. Ptito and colleagues), a physiotherapist (MUHC), an occupational therapist (MUHC), a speech therapist (MUHC), inpatient nurses (MNH), outpatient nurses at the MUHC and Notre Dame, and an MNH office secretary (Rubina Rangwala) who runs the clinic. The program also involves other physicians outside the MUHC (e.g. Dr. Bekhor (St Mary's), and Dr. Cloutier (South Shore, Sherbrooke), Drs. Melmed and Carlton (Jewish General Hospital), and others in the Quebec health network.

So far, roughly 200 patients have been operated on at the MUHC. Patients come from across the province of Quebec. The median age of these patients is 60 years. Typically, they

have had Parkinson's disease for 5-10 years, and have a disease severity of level 3-4 by the Hoen & Yahr staging, indicating "significant slowing of body movements, early impairment of equilibrium on walking or standing, and generalized dysfunction that is moderately severe."[4] All patients undergo a cognitive evaluation.

The rate of intracerebral hemmorhage from DBS at the MUHC is 0.5% over the last fifteen years, with no instances of permanent neurological deficit. There have been no suicides reported at the MUHC with DBS therapy. According to Dr. Sadikot, effects on verbal fluency are treatable using adjustment of current dose, electrode contact, and using L-Dopa or dopamine agonists.

5.1.2 Procedure

Each bilateral procedure lasts roughly 13 hours and is carried out over 2 days. After the surgery, patients are transferred to the ICU or a step-down unit for an average of 34 hours followed by an average hospital stay of 8.5 days. Patient's medication level is monitored to determine the appropriate L-dopa dose post-DBS. Patients are advised that there is a 2% risk of intracranial haemorrhage and a 7% risk of other adverse outcomes such as infection, erosion or malfunction of the device. After the surgery all patients are followed up at 6 month intervals.

5.1.3 Demand

At present, roughly 25 patients receive a new device during the months of January to September. No procedures are carried out during the remaining 3 months due to insufficient budget. With the current resources available at the MUHC (OR and personnel) Dr. Sadikot estimates that a further 15 patients could be operated on annually.

Currently, there are 18 patients awaiting primary implants. If procedures are again stopped for budgetary reasons, this list will increase even further. Patients currently wait about 6 months for the procedure. According to Dr. Sadikot, in the province of Quebec, an estimated 80 patients become eligible for DBS annually. Of these, roughly 10-15 are now treated in Quebec City. Thus, at the provincial level the estimated shortfall is about 40 patients per year.

5.1.4 Cost estimates

Cost estimates are summarized in Tables 5a & 5b.

Unit Costs

- The cost of a new DBS device (including battery, leads and extension) is $9,840. The cost is double for bilateral procedures ($19,680), which make up roughly two-thirds of all procedures. (Average device cost = $16,400).
- The operating cost, including one year follow-up, is $8,374.62 for a unilateral procedure and $12,379.90 for a bilateral procedure. (Average operating cost = $11,044.81)
- Thus the per patient cost to the MUHC for evaluation, surgery, hospitalization and one year follow-up, excluding professional fees, and excluding the costs of treating complications is 16,400 +11,044.81 = $27,444.81
- Since the life expectancy of the battery is 4-7 years, depending on the current delivered, reoperation for insertion of new batteries will be necessary at approximately 5.5 years. The cost would be approximately $8,647.27 for a unilateral replacement and $16,424.62 for a bilateral replacement. (Average replacement cost = $13,832.17)

Budget Impact

The budget impact of treating an additional 15 patients per year, including equipment costs at $246,000, would be $411,672.10 per year for the first five years, and $619,154.60 per year for the next five years.

NOTE. These estimates exclude the costs of treating procedure related complications. Also they relate only to costs for the first year of treatment. It is possible that there are cost savings to the health care system resulting from lower medication costs following DBS. However, these savings will not benefit the MUHC directly.

6 CONCLUSIONS

There is clear evidence that Deep Brain Stimulation improves motor function and sustains quality-of-life in patients with medically-resistant disease for a period of at least 5 years. It is

important that this intervention be performed by a skilled and experienced centre such as the MNH where expertise and experience have already been accumulated. Optimal selection and follow-up of patients is necessary to minimize the risk of adverse outcomes. There is an increasing waiting list in Quebec. To increase the turnover at the MNH by 15 patients per year would require $246,000 per year for equipment, or a total of approximately $411,672 (excluding costs of treating procedure related complications) per year during the first 5 years. Through reduction in medication costs there would be a significant saving from the point of view of the provincial health authority, but this would not affect the MUHC.

RECOMMENDATIONS

- **The committee recommends that this is a procedure that should be maintained and expanded at the MNH to the extent possible.**

- **When the MUHC renews its application to the health authorities for the necessary funds to support acquisition of DBS equipment, the following points could be stressed:**
    - **There is a significant wait time for this procedure, (currently 6 months to 1 year). It is estimated that in Quebec there is a need for approximately 35 additional procedures per year. An increase at the MNH of 15 patients per year would require an additional $246,000 per year for expandable equipment only.**
    - **DBS is a highly complicated procedure requiring a skilled and experienced team. To maintain such a team a high turnover is necessary and accordingly, the procedure should be restricted to very few centres. The MNH has been such a centre since 1985.**
    - **The current practice of operating for nine months (until the funds are expended), and then starting again three months later is highly inefficient and mitigates against achievement of the best operative results.**
    - **There is evidence that the cost to the provincial health administration (but not the MUHC) of maintaining a PD patient could decrease by approximately 50% following the procedure.**

REFERENCES

(1) Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79(4).

(2) Kleiner-Fisman G, Liang GS, Moberg PJ et al. Subthalamic nucleus deep brain stimulation for severe idiopathic dystonia: impact on severity, neuropsychological status, and quality of life. *J Neurosurg* 2007;107(1).

(3) Langston J, Widner H, Goetz C et al. Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 1992;7(1).

(4) Hoehn and Yahr Staging of Parkinson's Disease, Unified Parkinson's Disease Rating Scale (UPDRS), and Schwab and England Activities of Daily Living.2009(June 2).

(5) Fahn S, Elton R. Unified Parkinsons Disease Rating Scale. In: Fahn S, Marsden C, Goldstein M, Calne D, editors.Florham Park: Macmillan Healthcare Information; 1987.

(6) Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Qual Life Res* 1995;4(3):241-248.

(7) Jadad A, Moore R, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1).

(8) Deep Brain Stimulation for Parkinson’s Disease and Other Movement Disorders: Health Technology Literature Review. Ontario Ministry of Health; 2005.

(9) Deuschl G, Schade-Brittinger C, Krack P et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355(9).

(10) Schüpbach W, Maltête D, Houeto J et al. Neurosurgery at an earlier stage of Parkinson disease: a randomized, controlled trial. *Neurology* 2007;68(4).

(11) Weaver FM, Follett K, Stern M et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009;301(1).

(12) Witt K, Daniels C, Reiff J et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol* 2008;7(7).

(13) Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Arch Neurol* 2005;62(4).

(14) Burchiel KJ, Anderson VC, Favre J, Hammerstad JP. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. *Neurosurgery* 1999;45(6).

(15) Esselink RA, de Bie RM, de Haan RJ et al. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in Parkinson's disease: one year follow-up of a randomised observer-blind multi centre trial. *Acta Neurochir (Wien)* 2006;148(12).

(16) Merello M, Tenca E, Perez Lloret S et al. Prospective randomized 1-year follow-up comparison of bilateral subthalamotomy versus bilateral subthalamic stimulation and the combination of both in Parkinson's disease patients: a pilot study. *Br J Neurosurg* 2008;22(3).

(17) Rothlind JC, Cockshott RW, Starr PA, Marks WJ, Jr. Neuropsychological performance following staged bilateral pallidal or subthalamic nucleus deep brain stimulation for Parkinson's disease. *J Int Neuropsychol Soc* 2007;13(1).

(18) Smeding H, Esselink R, Schmand B et al. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD--a comparison of neuropsychological effects. *J Neurol* 2005;252(2).

(19) Wojtecki L, Timmermann L, Jorgens S et al. Frequency-dependent reciprocal modulation of verbal fluency and motor functions in subthalamic deep brain stimulation. *Arch Neurol* 2006;63(9).

(20) Siderowf A, Jaggi JL, Xie SX et al. Long-term effects of bilateral subthalamic nucleus stimulation on health-related quality of life in advanced Parkinson's disease. *Mov Disord* 2006;21(6).

(21) Wider C, Pollo C, Bloch J, Burkhard PR, Vingerhoets FJ. Long-term outcome of 50 consecutive Parkinson's disease patients treated with subthalamic deep brain stimulation. *Parkinsonism Relat Disord* 2008;14(2).

(22) Drapier S, Raoul S, Drapier D et al. Only physical aspects of quality of life are significantly improved by bilateral subthalamic stimulation in Parkinson's disease. *J Neurol* 2005;252(5).

(23) Erola T, Karinen P, Heikkinen E et al. Bilateral subthalamic nucleus stimulation improves health-related quality of life in Parkinsonian patients. *Parkinsonism Relat Disord* 2005;11(2).

(24) Gronchi-Perrin A, Viollier S, Ghika J et al. Does subthalamic nucleus deep brain stimulation really improve quality of life in Parkinson's disease? *Mov Disord* 2006;21(9).

(25) Montel S, Bungener C. What relation is there between deep brain stimulation and coping strategies in Parkinson's disease? *Mov Disord* 2008;23(12).

(26) Schupbach MW, Welter ML, Bonnet AM et al. Mortality in patients with Parkinson's disease treated by stimulation of the subthalamic nucleus. *Mov Disord* 2007;22(2).

(27) Voon V, Krack P, Lang AE et al. A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. *Brain* 2008;131(Pt 10).

(28) Meissner W, Schreiter D, Volkmann J et al. Deep brain stimulation in late stage Parkinson's disease: a retrospective cost analysis in Germany. *J Neurol* 2005;252(2).

(29) Valldeoriola F, Morsi O, Tolosa E, Rumia J, Marti MJ, Martinez-Martin P. Prospective comparative study on cost-effectiveness of subthalamic stimulation and best medical treatment in advanced Parkinson's disease. *Mov Disord* 2007;22(15).

(30) Berney A, Panisset M, Sadikot AF et al. Mood stability during acute stimulator challenge in Parkinson's disease patients under long-term treatment with subthalamic deep brain stimulation. *Mov Disord* 2007;22(8).

(31) Fraraccio M, Ptito A, Sadikot AF, Panisset M, Dagher A. Absence of cognitive deficits following deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Archives of Clinical Neuropsychology* 2008;23:399-408.

Table 1. Summary of results on treatment efficacy from RCTs comparing DBS to best medical therapy

Author, Year; Study country(s)	Total follow-up (mos)	Intervention (n=); % Female; Age(yr)=mean(SD)	Comparator (n=); % Female; Age(yr)=mean(SD)	Main outcome(s)	Jadad score; Adequacy of allocation concealment*	Funding source	Conclusion
Deuschl, 2006[10] & Witt, 2008;[13] Germany, Austria	6	DBS (n=78); 36%; Age=60.5(7.4)	medical therapy (n=78); 36%; Age=60.8(7.8)	L-dopa dose reduced more significantly (p<0.001) in the DBS (50%) than medical therapy group (10%). Improvements in UPDRS II,III subscales are significant for the DBS but not medical therapy group.	2; N/A	German Federal Ministry of Education and Research (01GI0201)	DBS improves patient quality of life with minor decrease in cognitive functions; it is safe in terms of neuropsychological and psychiatric outcomes.
Schupbach, 2007;[11] France	18	DBS (n=10); 30%; Age=48.4(3.3)	medical therapy (n=10); 50%; Age=48.5(3.0)	L-dopa dose reduced significantly (p<0.05) by 71%, 61%, and 57% at 6, 12, 18 months, respectively, whereas, the dose increased by 9%, 17%, and 12% in the medical therapy group. UPDRS II, IV measured off medication improved (p<0.05) for the DBS group. However, for the medical therapy group, UPDRS II, IV had worsened. PDQ-39 quality of life scores improved significantly (p<0.05) by 24% for DBS.	3; N/A	Medtronic Europe	Authors recommend considering DBS as a therapeutic option for early stage PD.
Weaver, 2009;[12] USA	6	GPi-DBS/DBS (n=61/60); 19%; Age=62.4(8.8)	medical therapy (n=134); 17.9%; Age=62.3(9.0)	L-dopa dose reduced by 23% and increased by 1% for the DBS and medical therapy group, respectively. 71% of DBS vs. 32% of medical therapy patients achieved clinically meaningful improvement in motor function (p<0.001). QoL improved by 20% and worsened by 1% for the DBS and medical therapy, respectively.	4; Unclear	National Institute of Neurological Disorders and Stroke, Medtronic Neuromodulation	At 6 months, DBS improves motor function, quality of life, and reduces L-dopa dose without troubling dyskinesia significantly compare to medical therapy. However, DBS is also associated with higher risks of complications and adverse events.

*Jadad scale: Score 0-5, with 0 equivalent to the lowest quality and 5 equivalent to the highest.

Abbreviations: RCT=Randomized Controlled Trial; DBS=Deep Brain Stimulation; mos=Months; n=Number of patients; N/A=Not applicable; SD=Standard deviation; yr=Year

Table 2. Summary of results on treatment efficacy from RCTs comparing DBS to therapies other than medical therapy

Author, Year; Study country(s)	Total follow-up (mos)	Intervention (n=); % Female; Age(yr)=mean(SD)	Comparator (n=); % Female; Age(yr)=mean(SD)	Main outcome(s)	Jadad score; Adequacy of allocation concealment*	Funding source	Conclusion
Burchiel, 1999[15] & Anderson, 2005;[14] USA	12	DBS (n=12); NR; Age=61(9)	GPi-DBS (n=11); NR; Age=54(12)	L-dopa usage decreased by 38% and 3% for the DBS and GPi-DBS groups, respectively (p=0.08). No statistical significant difference between GPi and DBS effects in terms of UPDRS III.	3; Unclear	Public Health Service grant 5 MO1 RR000334	Both GPi and STN are potential targets for optimal DBS treatment outcomes. It may be too early to exclude GPi as an option.
Merello, 2008;[17] Argentina	12	DBS (n=5); 46.7%; Age=62.1(3.4)	1. Bilateral subthalamotomy (n=5); 46.7%; Age=57.8(3.7) 2. Unilateral subthalamotomy + contralateral subthalamic stimulation (n=5); 46.7%; Age=63.0(3.8)	Bilateral DBS on average decreases L-dopa use by 69% at 6 months and 73% at 12 months (p<0.01). UPDRS subscales ADL (p<0.01), motor (p<0.009) and L-Dopa therapy complications (p<0.009) all showed significant improvement except mentation, which worsened (p<0.05).	2; N/A	Neuroscience department at the Raul Carrea Institute for Neurological Research, FLENI	Sample size too small to draw definitive conclusion, but in general, all three surgical methods improved motor function with no significant between-group difference.
Rothlind, 2007;[18] USA	6	DBS (n=19); 21.0%; Age=61.4(10.11)	GPi-DBS (n=23); 21.7%; Age=60.2(8.83)	UPDRS III improved by 37% in DBS group. Verbal fluency measured by phonemic sounds decreased significantly after DBS (p=0.021).	2; N/A	NR	Bilateral DBS has a negative effect on attention, working memory, processing speed, and verbal fluency but only showed statistically significant impact for verbal fluency. Follow-up period was too short, and a larger sample size is needed for future studies.
Smeding, 2005[19] & Esselink, 2006;[16] The Netherlands	12	DBS (n=20); 70%; Age=61(55-66)**	Pallidotomy (n=14); 57%; Age=62(57-68)**	L-dopa dose reduced by 33% and 12% for DBS and pallidotomy groups, respectively. UPDRS III improvement was significantly greater in the DBS group at both the off (53% improvement, p=0.002) and on phase (33% improvement, p<0.001) compared to pallidotomy.	3; N/A	Princess Beatrix fonds (MAR 99-0212)	Sample size was small to have adequate power. DBS has slightly more negative impacts than pallidotomy on neuropsychological outcomes but better motor function improvements.
Wojtecki, 2006;[20] Germany	Mean=28 (Range 3-51)	LF DBS (10Hz) (n=12); 25%; Age=64(22.76)	HF STB-DBS (130 Hz) (n=12); 25%; Age=64(22.76)	UPDRS III significantly better in the high frequency group (p<0.001). However, verbal fluency significantly better by using 10 Hz (p=0.04).	2; Unclear	Volkswagen Stiftung J/73240	Negative trend of HF DBS on verbal fluency while improving motor functions.

*Jadad scale: Score 0-5, with 0 being equivalent to the lowest quality and 5 being equivalent to the highest..
**Reported median (interquartile range)
Abbreviations: RCT=Randomized Controlled Trial; DBS=Deep Brain Stimulation; HF=High frequency; LF=Low frequency; mos=Months; n=Number of patients; N/A=Not applicable; NR=Not reported; SD=Standard deviation; yr=Year

Table 3. Complications and serious adverse events related to DBS for PD reported in RCTs

Author, Year; Study country(s); n=*; total follow-up	Death	Disability	Morbidity	Discomfort
Burchiel, 1999 & Anderson, 2005; USA; n=12; 12 mos		Dyskinesia n=1 (10) Transient anxiety n=2 (10) Transient delirium n=3 (10) Increased PD symptoms n=1 (10) Bradykinesia n=1 (10) Transient hallucination*** n=1 (10) Decreased cognitive functions n=1 (10)	Hematoma n=1 (10)	Lead reposition n=1 (10) Stimulation n=1 (10)§
Deuschl, 2006 & Witt, 2008; Germany, Austria; n=78; 6 mos	Intracerebral hematoma n=1 (1)† Suicide n=1 (1) Pneumonia‡ n=1 (1)	Depression n=4 (5) Psychosis n=4 (5) Severe loss of affect (apathy) n=1 (1) Post-operative confusion n=4 (5)	Intracerebral hematoma n=2 (3)† Infection at surgical site n=2 (3)	Subcutaneous seroma n=4 (5) Skin erosion n=3 (4) Extension strains in neck n=2 (3) Erroneous stimulator shut-off n=1 (1)
Weaver, 2009; USA; n=121**; 6 mos	Cerebral hemorrhage n=1 (1)	Nervous systems disorder n=15 (12) Fall n=31 (26) Gait disturbance n=12 (10) Balance disorder n=19 (16) Pain n=22 (18) Speech disorder n=20 (17) Dystonia n=19 (16) Bradykinesia n=17 (14) Dyskinesia n=12 (10) Motor dysfunction n=16 (13) Confusion n=18 (15) Surgical site pain (9)	Other infections n=2 (2) Headache n=23 (19) Cardiac disorder n=4 (3) Infection (10)	Lead migration/defective lead wire n=8 (7) Freezing phenomena n=12 (10)
Merello, 2008; Argentina; n=5; 12 mos	Hematoma 1 (20)	Irritability, excitation, paranoia, insomnia n=2 (40) Severe apathy n=1 (20)	Hematoma n=1 (20)	
Schupbach, 2007; France; n=10; 18 mos		Somatoform disorder n=1 (10)	Transient depression n=4 (40) Transient hypomania n=5 (50)	Lead reposition 1 (10)
Smeding, 2005 & Esselink, 2006; The Netherlands; n=20; 12 mos		Confusion n=4 (20) Emotional lability n=10 (50) Anxiety n=3 (15) Short-term memory disturbance n=4 (20)	Cerebrospinal fluid leakage n=1 (5)	Lead migration n=2 (10) Extension strains in neck n=3 (15) Drooling n=4 (20)

* RCT=Randomized Controlled Trial; DBS=Deep Brain Stimulation; n=Number of patient, whereas n=Number of events elsewhere in the table; **n=121 including balanced number of GPi and DBS patients; ***Resolved with the reduction of L-dopa dose. †One patient died following surgery; ‡Patient died 6 weeks following randomization; §One patient experienced increased dystonia, dysarthria, dysphasia, and hypophonia with stimulation frequency >30Hz. Also, in general, there were multiple incidences of unintentional switching off of the neurostimulation by external electromagnetic fields.

Table 4. Summary of results on quality of life from RCTs

Author, Year; Study country(s); Study design; n=; total follow-up	Age (mean(SD))	Disease duration	PDQ-39		Notes
			Baseline	Follow-up	
Deuschl, 2006[10] & Witt, 2008;[13] Germany, Austria	60.5(7.4)	13.8(6.3)	Mobility – 62.0(22.3) ADL – 55.0(23.6) Emotional wellbeing – 43.8(21.0) Stigma – 33.5(23.0) Social support – 20.7(20.8) Cognitions – 33.5(18.7) Communication – 37.6(19.8) Bodily discomfort – 48.0(22.2) TOTAL – 41.8(13.9)	Mobility – 46.8(28.0) ADL – 52.4(21.3) Emotional wellbeing – 40.7(21.3) Stigma – 31.3(22.7) Social support – 24.5(22.5) Cognitions – 33.4(16.7) Communication – 34.0(19.1) Bodily discomfort – 45.8(21.9) TOTAL – 31.8(16.3)	Quality of life improved significantly in the DBS group only.
Schupbach, 2007;[11] France; RCT; n=10; 18 mos	48.4(3.3)	7.2(1.2)	TOTAL – 35.4(24.4-51.5)*	TOTAL – 28.9(5.7-53.1)	Quality of life improved significantly in the DBS group only.
Weaver, 2009;[12] USA; RCT; n=121**; 6 mos	62.4(8.8)	12.4(5.8)	Mobility – 61.1(21.0) ADL – 55.0(17.6) Emotional wellbeing – 38.4(19.3) Stigma – 40.6(24.3) Social support – 26.9(19.6) Cognitions – 40.4(17.8) Communication – 45.3(20.0) Bodily discomfort – 51.2(21.2) TOTAL – 44.9(13.2)	Mobility – 48.8(25.2) ADL – 41.0(22.2) Emotional wellbeing – 32.6(19.5) Stigma – 28.2(23.7) Social support – 25.1(21.1) Cognitions – 36.7(20.4) Communication – 42.6(22.6) Bodily discomfort – 44.0(21.1) TOTAL – 37.3(16.0)	DBS patients improved significantly in 7 of 8 PDQ-39 subscales (except social support subscale) compared to medical therapy group. Older DBS patients showed significantly greater benefit in terms of mobility, ADL, and stigma subscales, than younger patients.

*Reporting median and interquartile range

**Including a balanced number of GPi and DBS patients

Abbreviations: mos=Months; n=Number of patients; SD=Standard deviation; yr=Year

Table 5a: Cost estimates for initial treatment and battery replacement for bilateral deep brain stimulation

	Item description	Unit cost ($)	Surgery		Battery replacement	
			Qty	Cost ($)*	Qty	Cost ($)*
Medical Imaging						
MRI	MSSS weighted unit estimation (Spine 3 levels)	100.67	3	302.00	-	-
Pre-op visit	Visit	35.53 $	2	71.06	1	35.53
Operating room						
Stage I & II	Patient hours	410.78	10.00	4,107.82	3.00	1,232.35 $
Stage III	Patient hours	410.78	4.00	1,643.13	-	-
Implants						
'- Generator	each	6,995.00	2	13,990.00	2	13,990.00
'- Lead	each	1,995.00	2	3,990.00	-	-
'- Extension	each	850.00	2	1,700.00	-	-
'- Programmer	each	-	1	-	-	-
Anaesthesia	Patient hours	110.78	14.00	1,550.98	3.00	332.35 $
Recovery room & ICU	hours	40.44 $	34	1,375.05	1	40.44
Post-op Nursing unit	days	379.21 $	8.5	3,223.28	2.0	758.42
Post-op visit	Visit	35.53 $	3	106.59	1	35.53
Total Device Cost				19,680.00		13,990.00
Total Operating Cost				12,379.90		2,434.62
Total Cost				**32,059.90**		**16,424.62**

* please note due to rounding to 2 decimal places some calculations may not add up exactly

Table 5b: Cost estimates for initial treatment and battery replacement for unilateral deep brain stimulation

			Surgery		Battery replacement	
	Item description	Unit cost ($)	Qty	Cost ($)*	Qty	Cost ($)
Medical Imaging						
MRI	MSSS weighted unit estimation (Spine 3 levels)	100.67	2	201.34	-	-
Pre-op visit	Visit	35.53 $	2	71.06	1	35.53
Operating room						
Stage I & II	Patient hours	410.78	7.00	2,875.46	1.5	616.17
Stage III	Patient hours	410.78	2.00	821.56	-	-
Implants						
'- Generator	each	6,995.00	1	6995.00	1	6,995.00
'- Lead	each	1,995.00	1	1995.00	-	-
'- Extension	each	850.00	1	850.00	-	-
'- Programmer	each	-	1	-	-	-
Anaesthesia	Patient hours	110.78	9.00	997.02	1.5	166.18
Recovery room & ICU	hours	40.44 $	16	647.04	1	40.44
Post-op Nursing unit	days	379.21 $	7	2,654.47	2.0	758.42
Post-op visit	Visit	35.53 $	3	106.59	1	35.53
Total Device Cost				9,840.00		6,995.00
Total Operating Cost				8,374.62		1,652.27
Total Cost				**18,214.62**		**8,647.27**

* please note due to rounding to 2 decimal places some calculations may not add up exactly

APPENDIX 1 Literature Search

Databases searched

- EMB Reviews – Cochrane Central Register of Controlled Trials,
- EMB Reviews – Cochrane Databse of Systematic Reviews,
- EMB Reviews – Health Technology Assessment
- EMB Reviews – NHS Economic Evaluation Database
- EMBASE
- Health and Psychosocial Instruments
- Ovid MEDLINE
- Ovid MEDLINE In-Process & Other Non-indexed Citations
- PsycINFO

Keywords used in the search included:

- Subthalamic nucleus
- Deep brain stimulation
- Neurostimulation
- Parkinson's disease
- Parkinson
- Dystonia
- Movement disorder
- Essential tremor
- Quality of life
- Daily living
- Adverse event
- Meta-analysis
- Systematic review
- Mortality
- Outcome
- Randomized controlled trials

Screening, study selection, data abstraction strategy

Three levels of screening were developed. First, potentially relevant articles were screened based on their titles and abstracts. At this level, any clinical studies on DBS and PD were retained for more detailed evaluation. Also, all systematic reviews, whether or not including a meta-analysis, were retained for reference screening.

At the second level screening, the reference sections of all systematic reviews were compared to the search returns, and the reviewer determined if there were additional potentially relevant articles to be included. At last, a citation that was deemed relevant was retrieved for full-text screening, where the citation was critically reviewed for its relevancy. Citations that passed the full-text screening were retained for data abstraction.

APPENDIX 2: Treatment outcome assessment

Table X: The Unified Parkinson's Disease Rating Scale

Subscale		Item no.	Scoring (for each item)
I.	Mentation	1-4	Scale 0-4; 0=Normal, 4=Worst
II.	Activities of daily living	5-17	Scale 0-4; 0=Normal, 4=Worst
III.	Motor function	18-31	Scale 0-4; 0=Normal, 4=Worst
IV.	Complications of therapy	A. Dyskinesia: 32-42 B. Clinical fluctuations: 36-39 C. Other complications: 40-42	A. 0-4; 0=Normal, 4=Worst B. "on" and "off" periods C. 0-1; 0=No, 1=Yes
V.	Modified Hoehn and Yahr Staging [of PD]	n/a	0-5, 0=No signs of disease, 5=Wheelchair-bound or bedridden unless aided
VI.	Schwab and England activities of daily living scale	n/a	0-100%; 0%=Vegetative functions & bedridden, 100%=Completely independent,

Table Y: Parkinson's Disease Questionnaire – 39 items Scoring chart

Subscale	no. of questions	Item no.	Highest score possible
Mobility	10	1-10	40
Activities of daily living (ADL)	6	11-16	24
Emotional wellbeing	6	17-22	24
Stigma	4	23-26	26
Social support	3	27-29	12
Cognitions	4	30-33	16
Communication	3	34-36	12
Bodily discomfort	3	37-39	12

Figure 2. Flowchart summarizing literature search