Deep brain stimulation for the symptoms of Parkinson's disease

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Assessment report

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Printed copies of the report can be obtained from:

The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 106
GPO Box 9848
Canberra ACT 2601

Enquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Omar Abdulwadud, Ms Sandra Younie, Dr Silva Zavarsek, Dr Veronica Pitt, Ms Amanda Weeks, Dr Renea Johnston, Ms Sharon King, Associate Professor Anthony Harris and Associate Professor Damien Jolley from the Monash Institute of Health Services Research and the Centre for Health Economics, Monash University and Ms Alex Lloyd from the Department of Health and Ageing. The report was edited by Dr Alana Mitchell, ScienceLink Pty Ltd. The report was endorsed by the Minister for Health and Ageing on 24 August 2006.

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Deep brain stimulation (DBS) involves the placement of electrical leads into one (unilateral) or both (bilateral) sides of the basal ganglia of the brain. The targets used for DBS are currently the thalamus, the subthalamic nucleus (STN) and the globus pallidus internus (GPi). Symptoms such as tremor or dyskinesias (abnormal involuntary movements) determine which part of the brain should be targeted. The DBS procedure is generally performed in two separate steps – implantation of leads followed by implantation of the neurostimulator to which the leads are connected.

For individuals with Parkinson's disease (PD) the key indication for DBS is that medical therapy no longer provides a smooth or sustained motor response. Before individuals proceed to DBS it is desirable for two neurologists to agree that all drug manipulations have been exhausted. DBS currently has interim funding on the Medicare Benefit Schedule.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Australian Government Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from Monash University was engaged to conduct a systematic review of literature on deep brain stimulation for the treatment of symptoms of Parkinson's disease. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of deep brain stimulation for the symptoms of Parkinson's disease

Clinical need

The incidence and prevalence of PD are estimated to be 85 and 289 per 100,000, respectively. Currently, DBS for the symptoms of PD is billed under a number of Medicare Benefit Schedule Item numbers. For the 2004-05 financial year, a total of 70 patients underwent surgery for unilateral DBS (MBS Item number 40850) or bilateral DBS (MBS Item number 40851).

Safety

The safety of DBS for the symptoms of PD was assessed from 42 case series. Findings from these studies indicated the risk associated with DBS, but did not allow quantitation of those risks compared with standard medical therapy (SMT). Some adverse events were reported to be transient or resolved with treatment; however a number were reported to be irreversible.

Nine studies, including a total of 244 participants, reported complications that occurred during surgery. One study reported that one of 25 (4.0%) participants experienced an ischaemic stroke. Haemorrhages and haematomas were reported to occur at a rate of between 2.1 (1/48 participants) and 7.1 (1/14 participants) per cent, and 2.1 (1/48 participants) to 12 per cent (3/25 participants), respectively, in individual studies.

Confusion was reported in two studies, with an incidence ranging from 6.9 (5/72 participants) to 21.4 (3/14 participants) per cent. Electrode repositioning/misplacement of electrodes/lead migration were reported to occur at a rate of between 6.1 (2/33 participants) and 14.3 (2/14 participants) per cent in three studies. One study reported that eight of 33 (21.2%) participants experienced transient intra-operative psychosis and another study reported that all of the eight participants enrolled experienced slight hand paresthesia.

Thirty-nine studies, including a total of 791 participants, reported hardware-related and stimulation- and target-related complications following surgery with follow-up to a maximum of 60 months. Of the hardware-related complications, nine studies reported complications relating to electrode and lead problems, with the events occurring at a rate of between 1.4 (2/141 participants) to 46.0 (6/13 participants) per cent in the individual studies. Other hardware-related adverse events included battery depletion and malfunctions that occurred at a rate of between 12.1 (4/33 participants) and 84.6 (11/13 participants) per cent in the individual studies. Three studies explicitly reported stimulation- and target-related complications that included ballism/chorea, blepharospasm, eyelid apraxia, increased weight and hypophonia.

Adverse events, described as being irreversible, were reported in 13 studies. Two studies reported weight gain in 2/6 participants (33.3%) and 29/33 participants (87.9%). One study each reported:

- cognitive changes and increased parkinsonian symptoms in 1/25 participants (8.0%);
- fluctuating cognitive, behavioural and mood disorders in 1/20 participants (5.0%);
- psychosis and severe depression in 5/77 participants (6.5%);
- dysarthria in two (4.2%), disabling dyskinesias in two (4.2%) and apraxia of eyelid opening in three (6.3%) of 48 participants;
- leg dysesthaesia in one (7.1%) and ataxia in one (7.1%) of 14 participants;
- hallucinations in five (10.2%), dementia in three (6.1%) and apathy in seven (14.3%) of 49 participants;
- worsening or development of dysphagia in 3/27 participants (11.1%);

- depression in 1/15 participants (6.7%);
- hypophonia in 12 (36.4%) and limb dystonia in one (3.0%) of 33 participants;
- confusion in 10/84 participants (11.9%); and
- intracerebral haemorrhage in 2/113 participants (1.8%).

Whilst these adverse events were reported to be irreversible in nature, weight gain for example would not require cessation of DBS. In fact, expert opinion suggests that weight gain may be a desirable outcome since weight loss is common in advanced PD. In addition, the reported adverse events may be reversible upon cessation of stimulation.

Three of the five Australian case series (of up to 153 participants with up to 49 months of follow-up) reported the need to reposition the electrodes in some patients. Another study reported that some patients had developed infection at either the pacemaker box or the extension wires going towards the brain. This problem was resolved following removal of the device and its replacement only after complete recovery from the infection. Some patients experienced confusion as a result of surgery and there were two cases of urinary tract infection that were also considered minor complications of surgery. The major complications relating to surgery were two cases of cerebral haemorrhage, of which one left the patient with significant cognitive sequelae that necessitated supervised care and the other led to death of the patient from intracerebral haemorrhage three weeks after the procedure. In relation to complications associated with stimulation, there were several reports of patients experiencing dysarthria and hypophonia and, to a lesser degree, emotional lability.

Assessment of the safety of DBS for the treatment of symptoms of PD was limited by:

- follow-up of participants to a maximum of only 60 months in the studies; and
- the lack of information about the comparative safety of DBS and SMT.

Expert opinion suggests that DBS is no less safe, and probably safer, than ablative surgery. Complications arising from DBS tend to be hardware related rather than neurologic.

Effectiveness

The effectiveness of DBS for the treatment of symptoms of PD was assessed from one double-blind crossover and three case-control studies. DBS appears to be effective for the treatment of PD symptoms, as statistically significant changes were observed between case and control participants in the United Parkinson's Disease Rating Scale (UPDRS) and Parkinson's Disease questionnaire (PDQ)-39SI scores. The double-blind crossover study demonstrated that DBS was reversible up to four years following surgery. In addition, this study also reported a statistically significant reduction in UPDRS III scores (which indicates increased motor control) from 43 points with stimulation OFF to 26 points with stimulation ON, in the absence of SMT. Similarly, one case-control study also reported a statistically significant reduction in UPDRS III scores in case participants (18.0 points) compared with control participants (41.7 points) at 24 months of follow-up when participants were not on medication (TIME-OFF).

Expert opinion suggests that this incremental difference of 23.7 points is highly clinically relevant for these patients. These results therefore show that DBS can ameliorate the symptoms of PD by smoothing out the motor fluctuations and avoiding severe ON periods polluted by dyskinesia and severe OFF periods when the patient experiences the symptoms of PD such as tremor, rigidity and akinesia, as measured by the UPDRS Motor section.

Two case-control studies also reported significant reductions in the daily OFF rate (refers to the time where medication is not effective). One study reported a reduction in the daily OFF rate from 46.1 per cent at baseline to 5.2 per cent at 24 months of follow-up for participants undergoing DBS, whilst those who continued on SMT showed a slight increase in daily OFF rates between baseline and 24 months follow-up. Another study also reported a reduction in the daily OFF rate from 31.0 per cent at baseline to zero per cent at 6 months follow-up, however this study did not report the daily OFF rate for control participants. These results indicate that DBS can ameliorate the symptoms of PD by smoothing out the motor fluctuations during periods when SMT is not effective and allows a significantly greater proportion of the day when the symptoms of PD are maintained at levels similar to those when medication is effective.

The three case-control studies indicated that DBS also reduced the levodopa equivalent daily dose (LEDD) required to maintain control of the symptoms of PD. This reduction may also significantly decrease some of the side effects associated with prolonged high-dose levodopa treatment. However, the assessment of the effectiveness of DBS for the treatment of symptoms of PD was limited by the following:

- the relatively small number of individuals who have been analysed;
- significant losses to follow-up in some studies; and
- follow-up of participants to a maximum of only 48 months in the studies.

Nevertheless, the data reported from these studies are supported by those in the systematic review of the case series literature that included 38 individual studies and up to 471 participants. The review indicated that DBS allowed the maintenance of abilities to perform activities and increased motor function in the absence of SMT. In addition, patients receiving DBS required lower LEDDs to maintain their ability to perform activities of daily living and increase motor functions over time. Whilst the magnitude of this effect attributable to DBS is difficult to quantitate due to a lack of a comparator group in the studies included in the published review, the results reported in the double-blind crossover and case control studies support the suggestion that these positive effects were attributable to DBS.

Cost-effectiveness

It has been estimated that the incremental costs of the STN DBS procedure under interim MBS funding is approximately $67,475–$73,204 discounted per patient, with potential additional discounted costs of approximately $9,956 as a result of complications of the surgery over five years. This cost includes the direct costs of surgery (hardware, cost of the procedure, post-operative monitoring, in-patient stay as well as adverse events attributable to the procedure and hardware). It may be slightly underestimated,

depending on the extent to which psychological testing is included in the pre-surgery workup, which may vary between surgical centres.

The incremental costs are higher than were estimated in the previous MSAC evaluation because of a change in comparator from ablative surgery to SMT. Ablative surgery and DBS have surgical costs in common, resulting in a narrower incremental cost difference. However, this estimate of the cost of the insertion of a DBS system is consistent with that provided in the previous MSAC assessment of $60,917–$75,808 per patient.

The three case-control studies reported reductions in the LEDD. Using case series data as the basis, this reduction in pharmacotherapy is estimated to result in savings in drug costs of about $57,200 discounted over a five-year period. Possible cost savings from a reduced rate of falls between those on DBS and those on SMT due to improved control of motor symptoms could not be quantified.

Quality of life (QoL) as an economic variable could not be calculated. The evidence for STN DBS on patient self-reported QoL measures is not straightforward since items measuring physical wellbeing improved significantly at least two years post-surgery but those measuring emotional wellbeing, social support, cognition and communication showed no strong evidence of any improvement.

The extra cost of an improvement in the UPDRS III score of 23.7 points is estimated at $20,232–$25,961 if the savings in pharmacotherapy are deducted from the total cost of the procedure, including the potential costs of complications.

Readers are advised that the MSAC recommendation herein is dependent on both the results presented in the current assessment report and those of the previous MSAC report assessing the safety, effectiveness and cost-effectiveness of DBS (MSAC 2001). The MSAC 2001 report can be accessed via: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1031-1/$FILE/msac1031.pdf.

Recommendation

MSAC has considered the safety, effectiveness and cost-effectiveness of deep brain stimulation for refractory severe Parkinson's disease compared with optimal medical therapy.

MSAC finds that there is sufficient evidence of safety and effectiveness, and robust information on cost-effectiveness is unlikely to emerge but the total cost is acceptable for patients in whom other therapies are insufficient.

MSAC recommends that public funding be provided for patients with Parkinson's disease where their response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations.

The Minister for Health and Ageing accepted this recommendation on 24 August 2006.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of deep brain stimulation (DBS), a therapeutic technique for the treatment of symptoms in individuals with Parkinson's disease (PD). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

In April 2001, MSAC reviewed the evidence associated with DBS for managing the symptoms of PD (MSAC 2001). Based on the evidence at that time, MSAC recommended interim funding for DBS for three years. Interim funding was subsequently extended to April 2006 to allow a review of any new evidence on the effectiveness of DBS for the symptoms of PD. In October 2002, an addendum review that summarised the evidence published since the first 2001 MSAC assessment report was submitted to the Department of Health and Ageing. The current review was sought as a result of the interim funding coming to completion and to examine any evidence on the effectiveness of DBS published since the previous report.

Readers are advised that the MSAC recommendation herein is dependent on both the results presented in the current assessment report and those of the previous MSAC report assessing the safety, effectiveness and cost-effectiveness of DBS (MSAC 2001). The MSAC 2001 report can be accessed via: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1031-1/$FILE/msac1031.pdf.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for DBS for the treatment of symptoms of PD.

Background

Deep brain stimulation for symptoms of Parkinson's disease

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by the progressive death of selected but heterogeneous populations of neurons (Lang & Lozano 1998). The pattern of loss of dopaminergic cells in the substantia nigra of the midbrain is relatively specific for PD. As these dopaminergic cells degenerate, there is insufficient dopamine to maintain normal functioning. The symptoms and progression of PD vary among individuals. Symptoms include rigidity, tremor, bradykinesia and postural instability. The disease is currently incurable; however, it can be managed and those with PD can live independent, productive lives.

Dopaminergic medication is used as a first-line treatment for reducing the primary symptoms of PD. However, medication can become less effective as the disorder progresses and has the potential to produce adverse effects such as dyskinesias and motor fluctuations. When response fluctuations become increasingly difficult to manage medically, individuals with PD can spend their waking days transitioning between ON time (good motor function), ON time with dyskinesias (good motor function disabled by dyskinesia) and OFF time (disabled by disease symptoms). Individuals whose symptoms are inadequately controlled by medication may benefit from surgical treatment.

Ablative surgery and DBS have been the main surgical treatments for PD. Ablative surgery includes pallidotomy, thalamotomy and sub-thalamotomy, which destroy the globus pallidus (GPi), thalamic nucleus and subthalamic nucleus (STN), respectively. Once the suitable target tissue has been located, it is destroyed by a radio frequency or thermocoagulation method. Expert opinion suggests that ablative procedures are rarely performed in Australia. Although ablative surgery is still available as a treatment option for individuals with PD in Australia, it is generally restricted to those who are not suitable for DBS and other highly selected cases. Ablative surgery has largely been replaced by DBS, in part because DBS is potentially reversible and is perceived to be associated with improved safety and effectiveness and in part because ablative surgery is irreversible and regarded as having limited effectiveness and significant safety concerns.

DBS involves the stimulation by electrodes connected to an implantable stimulator of the same tissue targeted in ablative surgery. Explicitly, electrical leads are placed into one (unilateral) or both (bilateral) sides of the basal ganglia of the brain. The three targets for DBS in the basal ganglia are the thalamus, STN and the GPi. The target site chosen for DBS is dependent on specific PD symptoms. The key indication of DBS for those with PD is that medical therapy no longer provides a smooth or sustained motor response.

Rating scales used for Parkinson's disease

United Parkinson's disease rating scale (UPDRS)

The United Parkinson's Disease Rating Scale (UPDRS) is a tool used to follow the longitudinal course of PD. It comprises four sections:

- Part I: Mentation, behaviour and mood
- Part II: Activity of daily living (ADL)
- Part III: Motor
- Part IV: Complications of therapy

The UPDRS sections are evaluated by interview and some sections require multiple grades assigned to each extremity. A total of 199 points may be assigned where 199 represents total disability and zero represents no disability. Table 1 presents the sections of the UPDRS and the areas of ability/disability that are assessed within each. The areas of ability are rated between zero and four, where zero indicates absence of the symptom or the individual's ability to complete a task as normal and four represents frequent or severe symptoms or the inability to complete a particular task.

Table 1 United Parkinson's disease rating scale (UPDRS)

Section	Areas of ability/disability
I: Mentation, behaviour, mood	Intellectual impairment Thought disorder Depression Motivation/initiative
II: Activities of daily living	Speech Salivation Swallowing Handwriting Cutting food/handling utensils Dressing Hygiene Turning in bed/adjusting bed clothes Falling – unrelated to freezing Freezing when walking Walking Tremor Sensory complaints related to Parkinsonism

Table 1 (cont'd) United Parkinson's disease rating scale (UPDRS)

Section	Areas of ability/disability
III: Motor exam	Speech Facial expression Tremor at rest Face Right and left upper and lower extremities Action or postural tremor Right and left upper extremities Rigidity Neck Right and left upper and lower extremities Finger taps Right and left Hand movements Right and left Rapid alternating movements (pronate and supinate hands) Right and left Leg agility (tap heel on ground, amplitude should be 3 inches) Right and left Arising from chair Posture Gait Postural stability Body bradykinesia/hypokinesia
IV: Complications of therapy	Dyskinesias Duration Disability Painful dyskinesias Presence of early morning dystonia Clinical fluctuations Predictability of OFF periods Sudden onset OFF periods Proportion of day in OFF period Other complications Eating disturbances Sleeping disturbances Symptomatic orthostasis

Source: The National Parkinson Foundation, www.parkinson.org [IAccessed 11 September 2005]

Despite the UPDRS rating scale being a subjective measure, dependent on the interviewer and the timing, various studies have shown that the intra-observer and inter-observer validity and reliability of the UPDRS III scale are adequate both in early (Siderowf et al 2002) and advanced (Metman et al 2004) PD. Most interviewers who use the UPDRS scale are experienced such that measured differences are real; however the clinical significance of the measured differences will vary among individuals with PD if some variables in the UPDRS are more important to certain individuals.

Expert opinion suggests that the total UPDRS score could increase by 10 points per year for some patients. Data from a randomised controlled trial (RCT) comparing the effectiveness of anti-parkinsonian medication in early PD support this expert opinion (The Parkinson Study Group 1993). The average annual rate of decline in the total UPDRS scores for individuals assigned to placebo in this trial was a mean of 14.02± a standard deviation (SD) of 12.32 points. For those assigned to the anti-parkinsonian medication group, the average annual rate of decline in the total UPDRS scores ranged from 7.00±10.76 to 15.16±16.12 points (The Parkinson Study Group 1993).

The results of a study by Goetz et al (2000) on the rate of progression of clinical impairment in individuals with PD treated with levodopa indicated differences in the progression of symptoms of PD as measured by the UPDRS according to the stage of disease. The study included a random sample of 100 individuals selected from a larger group on the basis of their initial Hoehn & Yahr stage (Stage II and Stage III, see Table 2) on presentation at the study centre. All individuals (50 Stage II and 50 Stage III) were assessed in the medication ON state with annual measurements of UPDRS motor scores, dyskinesia ratings and anti-Parkinsonian medication doses over four years. Individuals entering the study at Hoehn & Yahr Stage II showed no significant change in the mean UPDRS motor scores from baseline (27.8±1.4 points) to four years (28.3±1.8 points). However, in the same group there were significant increases in dyskinesias and dopaminergic medications that were progressive over each year of the four-year follow-up.

For individuals who entered the study at Hoehn & Yahr Stage III, the mean UPDRS motor scores progressed significantly from 38.1±1.4 points at baseline to 41.7±2.0 points at four years ($p=0.0006$). The individuals in this group also had an increase in dyskinesia that occurred in the first year of the study and remained stable thereafter. The increase in dyskinesias observed between baseline and the four-year follow-up was not statistically significant. As for the Stage II participants, those entering the study at Stage III had a significant increase in the doses of dopaminergic medication (Goetz et al 2000).

The six clinical domains of the UPDRS motor section – axial bradykinesia, right bradykinesia, left bradykinesia, rigidity, rest tremor and action tremor – were analysed to examine if any specific parkinsonian symptoms preferentially progressed over the study period. For participants entering the study at Stage II, in which no overall decline in motor symptoms was observed, a significant decline in axial bradykinesia (including speech, facial expression, arising from a chair, posture, gait, postural stability and body bradykinesia) was observed. Similarly, for participants entering the study at Stage III, there was a significant decline in axial bradykinesia in addition to right and left bradykinesia. There was no significant decline in rigidity, rest tremor or action tremor in Stage II or Stage III participants over the four-year follow-up (Goetz et al 2000).

Louis et al (1999) reported on a large community-based cohort of individuals with PD who were evaluated annually for up to eight years (mean of 3.3 years following baseline assessment) for their extrapyramidal signs using the UPDRS III motor section. The cohort included 237 individuals with PD who had one baseline visit and at least one year of follow-up. The annual rate of increase in the total extrapyramidal sign score (UPDRS III) was 1.5 points (1.5%), and among those individuals in the cohort who died, the total extrapyramidal sign score increased by 3.6 points (3.6%) annually. When the cohort was stratified into those with short (≤3 years) and long (>3 years) duration of disease, the

progression of the extrapyramidal sign score was greater in the former group (1.9 points annually) than the latter (1.4 points annually).

Further analyses subdivided the extrapyramidal sign score into the subscores tremor, bradykinesia, rigidity, and gait and balance. All but the tremor subscore increased at a significant annual rate: bradykinesia (0.6 of a possible 28 points), rigidity (0.4 of a possible 20 points), and gait and balance (0.5 of a possible 16 points) (Louis et al 1999). Louis et al (1999) also reported that the baseline variables dementia, low activities of daily living scores and long disease duration were predictors of the extrapyramidal sign score at each yearly visit. In a separate study of 297 patients followed up for a mean of 6.36 years, all components of UPDRS parts I and II, except for handwriting, worsened during the observation period (Jankovic & Kapadia 2001).

Table 2 Hoehn & Yahr staging of PD

Stage	Symptoms
I	1. Signs and symptoms on one side only 2. Symptoms mild 3. Symptoms inconvenient but not disabling 4. Usually presents with tremor of one limb 5. Friends have noticed change in posture, locomotion and facial expression
II	1. Symptoms are bilateral 2. Minimal disability 3. Posture and gait affected
III	1. Significant slowing of body movements 2. Early impairment of equilibrium on walking or standing 3. Generalised dysfunction that is moderately severe
IV	1. Severe symptoms 2. Can still walk to a limited extent 3. Rigidity and bradykinesia 4. No longer able to live alone 5. Tremor may be less than earlier stages
V	1. Cachectic stage 2. Invalidism complete 3. Cannot stand or walk 4. Requires constant nursing care

Source: The National Parkinson Foundation, www.parkinson.org [Accessed 11 September 2005]

Parkinson's disease questionnaire summary index (PDQ-39SI)

The Parkinson's disease questionnaire (PDQ) was developed on the basis of interviews with individuals with PD and a number of large-scale surveys. It contains eight dimensions (Jenkinson et al 1997; see Table 3). The questionnaire is a disease-specific measure of subjective health status and produces a profile of scores indicating the impact of the disease. The summary index (SI) was developed from the questionnaire and provides an indication of the global health impact of PD (Jenkinson et al 1997).

Table 3 Dimensions and number of items in each dimension of the PDQ-39SI

Dimension	Number of items
Mobility	10
Activities of daily living	6
Emotional well-being	6
Stigma	4
Social support	3
Cognition	4
Communication	3
Bodily discomfort	5

Source: Jenkinson et al (1997)

The procedure

Deep brain stimulation involves the placement of electrical leads into one (unilateral) or both (bilateral) sides of the basal ganglia of the brain. The targets for DBS are the thalamus, the sub-thalamic nucleus (STN) and the globus pallidus internus (GPi). The target site chosen for DBS is dependent on specific PD symptoms to be treated. For example:

- thalamic DBS is used predominantly for tremor (Nicholson & Milne 1999, Starr et al 1998);
- STN DBS is used for tremor, dyskinesia, rigidity, bradykinesia, akinesia, speech difficulties and freezing in the OFF state (Nicholson & Milne 1999);
- GPi DBS is used for dyskinesias, reduction in OFF state (to increase overall mobility), tremor rigidity, bradykinesia and akinesia (Nicholson & Milne 1999).

It is important to note however, that the exact target location and indication for each of these procedures has not been standardised (Starr et al 1998).

The DBS procedure is generally performed in two separate steps – implantation of leads followed by implantation of the neurostimulator to which the leads are connected. Patients need to be tested initially for their responsiveness to therapy. This is accomplished by implanting a lead at the relevant site using a combination of stereotactic techniques such as image-guided stereotactic localisation and physiological techniques such as microelectrode mapping or macrostimulation. The implantation procedure is generally performed under local anaesthetic. The placement of the electrode at a particular site is determined by the patient's response to stimulation (involving physical evaluation of the lower limbs and face muscles) and interpretation of the microelectrode recording data. Once the target that elicits the best response has been localised, the testing electrodes are removed and replaced with permanent leads.

From 12 hours (Merello et al 1999) to several days (Schuurman et al 2000) after surgery to position the electrodes, the neurostimulator is implanted below the clavicle while the patient is fully anaesthetised. Once the neurostimulator is internalised by subcutaneous tunnelling, the neurologist uses an external programming unit to adjust the stimulation parameters (pulse width, stimulation amplitude and stimulation frequency) to the patient's needs. These stimulation parameters typically have a pulse width of 60–120 μs,

amplitude of 1–3 V and frequency of 135–185 Hz. The patient may turn the stimulator on or off, according to the physician's instructions, with an external magnet.

Intended purpose

For individuals with PD, the key indication of DBS is that medical therapy no longer provides a smooth or sustained motor response. Further indications such as tremor and dyskinesias differentiate which part of the brain should be targeted. For example, thalamic and STN DBS is indicated for individuals who have responded to medication, but whose response has been contaminated by severe unpredictable motor fluctuations (such as tremor that interferes with writing and eating). For those with PD and drug-induced dyskinesias and bradykinesia, the GPi is considered to be the most appropriate site for stimulation. Before patients proceed to DBS, it is desirable that two neurologists agree that all drug manipulations have been exhausted. It is expected that neurosurgeons will perform the DBS procedure.

Contraindications for DBS include dementia, extensive brain atrophy or systemic medical problems that increase medical risk (such as coagulopathy or untreated chronic hypertension). DBS should not be undertaken in patients who are unable or unwilling to comply with routine follow-up, since stimulation parameters require modification both in the first instance and with continuation of treatment. Since the DBS device is indwelling, a stimulator should not be placed in those with concurrent infection.

Clinical need / burden of disease

An extensive literature search of the following databases was undertaken to update the previous data (MSAC 2001) relating to the prevalence and burden of disease of PD in Australia:

- Medline
- World Health Organization
- Australian Institute of Health and Welfare
- Australian Bureau of Statistics
- Victorian Department of Human Services
- Department of Health, South Australia
- Queensland Health
- Department of Health, Western Australia
- NSW Health
- BEACH data cube
- Interactive national hospital morbidity data

In addition, a general search of the Internet to identify possible data sources was undertaken using www.google.com. The search terms used included Parkinson disease, data, incidence, prevalence, burden of disease (BOD), deaths, years of life lost (YLL), disability adjusted life years (DALY) and mortality.

There has been little in the way of updates of BOD data for PD nationally or internationally since the previous report (MSAC 2001). Updated BOD data are often limited to broader categories of illness and in the case of PD are normally coded as Alzheimer's/Dementia or Neurological/Nervous System Diseases.

Table 4 lists Australian data for incidence; years lived with disability, duration of illness and deaths using the 1996 Australian Burden of Disease Study.

Table 4 Australian data for incidence, years lived with disability, duration of illness and deaths due to PD

Gender	Incidence (per 100,000)	Prevalence (per 100,000)	Years lived with disability (per 100,000)	Duration (years)	Deaths (per 100,000)
Male	35	127	92.7	6.0	4.4
Female	50	162	132.7	6.0	3.1
Total	85	289	224.4	–	7.5

Source: Mathers et al (1999)

The accuracy of figures for incidence and prevalence is questionable due to their being no definitive test for PD. The mean age of onset of PD is 73.3 years for men and 76.5 years for women (Mathers et al 1999). Diagnosis before the age of 40 is rare (Parkinson's Australia 2005). There appear to be no race-related differences.

There were 968 deaths attributed to PD in Australia in 2002 (representing 0.7 per cent of all deaths for that year), of these, 63 per cent were male (AIHW 2005). In 1996, the total number of deaths was 686, representing 0.5 per cent of all deaths for that year (Mathers et al 1999). The number of deaths attributed to PD may be significantly underestimated because the complications of the immobility of PD (eg pneumonia and falls) and of the disease itself (eg late dementia) or its treatment (eg cognitive changes or hypotension) are probably recorded as the cause of death rather than PD.

Currently, DBS for the symptoms of PD is billed under a number of Medicare Benefit Schedule Item numbers (see the 'Current reimbursement arrangement' section of this report). Whilst a number of MBS Item numbers are used for DBS, numbers 40850 and 40851 refer to the unilateral and bilateral placement of electrodes, respectively, and thus represent individual patients. Table 5 presents the number of services performed since the implementation of interim funding for DBS in 2001 for MBS Item numbers 40850 and 40851. The unilateral or bilateral DBS procedure was undertaken in 70 patients in the 2004-05 financial year. Since the implementation of MBS funding for DBS, 177 patients have undergone the procedure. Expert opinion estimates that 10 to 20 per cent of individuals who are eligible to undergo the procedure would receive it.

Table 5 Total number of services for unilateral and bilateral DBS

Financial Year	MBS item number		Total
	40850 – Unilateral DBS	40851 – Bilateral DBS	
2001–2002	11	0	11
2002–2003	49	0	49
2003–2004	10	37	47
2004–2005	13	57	70
Total	83	94	177

Source: http://www.medicareaustralia.gov.au [Accessed 12 September 2005]

Existing procedures

Levodopa combined with adjunct medical therapy is the standard medical treatment (SMT) for individuals with PD. However, prolonged use of levodopa can cause disabling motor fluctuations and dyskinesias. When medication is no longer effective or produces unacceptable side effects, surgical treatments may be a possible alternative.

The main surgical treatments for PD are ablative surgery and DBS. Ablative surgery can include pallidotomy, thalamotomy and subthalamotomy. These procedures involve destroying the GPi, thalamic nucleus and STN, respectively. A variety of sites can be used within these targets, such as the posterolateral or posteroventral areas of the GPi and the ventral intermediate or venterolateral nucleus of the thalamus. Once the suitable target tissue has been located, it is destroyed using such methods as radiofrequency ablation and thermocoagulation. Expert opinion states that these procedures are rarely performed in Australia.

As described in the previous section, DBS involves the stimulation of the same tissue targeted in ablative surgery using electrodes connected to an implanted stimulator. Although stimulation has hitherto concentrated on the STN and GPi, it would appear that the former is becoming the preferred target (Nicholson & Milne 1999).

Comparator

The only alternative to DBS in Australia is SMT. Therefore, studies in which a comparison was made between DBS and SMT, and the implanted device being turned ON and turned OFF were considered for this review. Unlike for the previous MSAC report (MSAC 2001), ablative surgery is no longer considered an appropriate comparator as expert opinion suggests that it is rarely performed in Australia. Ablative surgery as a treatment option for individuals with PD in Australia is generally restricted to those who require surgery for PD but are not suitable for DBS, and other highly selected cases. Ablative surgery has largely been replaced by DBS, in part because DBS is potentially reversible and is perceived to be associated with improved safety and effectiveness and in part because ablative surgery is irreversible and regarded as having limited effectiveness and significant safety concerns.

Marketing status of the device / technology

The medical devices used for DBS are either registered or listed on the Australian Register of Therapeutic Goods, which is administered by the Therapeutic Goods Administration (TGA) agency. The devices used for this procedure can be divided into leads, extension, implantable pulse generators (IPGs), intra-operative positioning and testing and patient-therapy control (Table 6). In addition to these devices, the neurologist will use the N'Vision programmer (AUST R90520/104700) to program the IPG.

Table 6 TGA registrations and listing numbers of medical devices used for DBS

Device	ARTG Number	Description
Leads		
3387	AUST R 56143	Four Pt-Ir contacts 1.5 mm apart Each 1.5 mm long, total span 10.5 mm, includes a burrhole ring and cap
3389	AUST R 82095	Four Pt-Ir contacts 0.5 mm apart Each 1.5 mm long, total span 7.5 mm, includes a burrhole ring and cap
3550-09	AUST L 65882	Accessory kit and plug for use with Kinetra for a unilateral system
Extension		
7482	AUST R 96927	Low profile low impedance extension kit
Implantable pulse generator		
Kinetra Model 7428	AUST R 75395	Dual channel neurostimulator
Soletra Model 7426	AUST R 80645	Single channel neurostimulator
Intra-operative positioning and testing		
34680	Special access	Microtargeting electrodes, box of 5
9013C0502	AUST L 74222	Sterile MER connecting cable
Patient therapy control		
7436	AUST R 79950	Access Therapy Controller for patient control of Kinetra within preset limits
7438	AUST R 80126	Access Therapy Controller for patient control of Soletra within preset limits

The TGA has promoted the devices from Listed to Registered without testing because they have been used for many years in the Australian setting.

Current reimbursement arrangement

Deep brain stimulation is currently billed under Medicare Benefits Schedule (MBS) Item numbers:

- 40850: Deep Brain Stimulation for Parkinson's disease (unilateral), functional stereotactic procedure including computer assisted anatomical localisation, physiological localisation including twist drill, burr holes craniotomy or craniectomy and insertion of electrodes (Anaes) (Assist).
- 40851: Deep Brain Stimulation for Parkinson's disease (bilateral), functional stereotactic procedure including computer assisted anatomical localisation,

physiological localisation including twist drill, burr hole craniotomy or craniectomy and insertion of electrodes (Anaes) (Assist).

- 40852: Deep Brain Stimulation for Parkinson's disease (unilateral), subcutaneous placement of neurostimulator receiver or pulse generator (Anaes) (Assist).
- 40854: Deep Brain Stimulation for Parkinson's disease (unilateral), revision or removal of brain electrode (Anaes).
- 40856: Deep Brain Stimulation for Parkinson's disease (unilateral), removal or replacement of neurostimulator receiver or pulse generator (Anaes).
- 40858: Deep Brain Stimulation of Parkinson's disease (unilateral), placement, removal or replacement of extension lead (Anaes).
- 40860: Deep Brain Stimulation for Parkinson's disease (unilateral) target localisation incorporating anatomical and physiological techniques, including intra-operative clinical evaluation, for the insertion of a single neurostimulation wire (Anaes).
- 40862: Deep Brain Stimulation for Parkinson's disease, electronic analysis and programming of neurostimulator pulse generator (Anaes).

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period between 2002 and 2005. All searches were conducted on 4 August 2005 using the electronic databases listed in Table 7.

Table 7 Electronic databases searched in this review

Database	Period covered
Australasian Medical Index	2002–August 2005
Biological Abstracts (OVID)	2002–August 2005
CINAHL (OVID)	2002–August 2005
Cochrane Library	2002–August 2005
EMBASE (OVID)	2002–August 2005
Medline (OVID)	2002–August 2005
Medline in process and other non-indexed citations (OVID)	Update to 4 August

Several search strategies were required for coverage of all aspects needed for this topic. The main areas were safety, effectiveness and cost-effectiveness.

All terms that can be used to describe the patient group, the intervention and the comparators were identified. This set of words (the core terms) formed the basis of our searching (Appendix C).

For safety, the terms for safety, complications and adverse events were combined with the intervention terms. For effectiveness, the core terms were filtered with a Cochrane Collaboration hedge to identify high-level evidence.

Internet sites from health technology assessments (HTAs), clinical trials registers and other relevant professional bodies were also searched (Appendix D).

Selection criteria

Criteria developed *a priori* to determine eligibility of relevant studies (Table 8) were based on those agreed upon by MSAC and the members of the Advisory Panel.

Table 8 *A priori* selection criteria

What is the safety, effectiveness and cost-effectiveness of DBS to manage symptoms of PD in adults who have failed to respond to standard medical treatment or accompanied by severe side effects?		
Characteristics	Inclusion	Exclusion
Participants	Adults with severe PD for whom medication is no longer effective or produces severe side effects. The results of studies that enrolled mixed populations of participants, ie PD and essential tremor, were included if they adequately reported data for participants with PD separately	PD not refractory to drug treatment (ie trials that recruited adults with severe PD who were responsive to medication were excluded) Contraindications for DBS include dementia, extensive brain atrophy or systemic medical problems that increase medical risk (such as coagulopathy or untreated chronic hypertension). DBS should not be undertaken in patients who are unable or unwilling to comply with routine follow-up, since stimulation parameters may need to be modified both in the first instance and as treatment continues. Since the DBS device is indwelling, a stimulator should not be placed in those with concurrent infection
Intervention	DBS: Pallidal or sub-thalamic	• Combined DBS and contralateral thalamotomy or pallidotomy • DBS in the thalamus since it is not widely used for patients with PD
Comparators	• SMT or • Electrode implanted, stimulator OFF plus SMT	• Studies not using the comparators of interest • Ablative surgery as it is not commonly used in Australia
Outcomes	PD symptoms assessed by UPDRS, Hoehn & Yahr scale, duration of response (eg time when there is absence of shaking). Participant-based outcomes such as quality of life, drug usage and adverse effects. In addition, the cost of DBS and SMT or placebo were compared UPDRS, Off-medication pre- and post-operative and QALY	Physiological outcomes alone
Study design (Methodology)	For effectiveness of DBS: HTAs, systematic reviews, meta-analyses and RCTs were sought. As these were unavailable, comparative studies were assessed For safety of DBS: All study designs reporting adverse events associated with the application of DBS were considered for inclusion	For effectiveness: Narrative reviews, editorials, other opinion pieces, articles identified as preliminary reports when results are published in later versions, articles in abstract form only, case reports and case series which do not explicitly report that subjects were consecutively selected were excluded
Publication and year	English-language articles, or well-designed RCTs published in any language after 2002 (DBS report updated in October 2002)	Studies published before 2002 as they were included in the October 2002 update report submitted to the Department of Health & Ageing

Abbreviation: QALY, quality-adjusted life years

Safety

Studies identified after the application of the safety filter to the search strategy were retrieved and examined. Adverse event data relating to DBS for the symptoms of PD were extracted and tabulated. In the review of safety, case reports or any comparative studies were included because information indicating whether or not a procedure is safe is as important as how safe it is compared to the alternatives.

Effectiveness

Assessment of validity

The most rigorous study design for assessing the validity of a therapy is considered to be an RCT that compares outcomes in a group of patients who have undergone the therapy in question with outcomes in a group of patients who have not (Guyatt et al 1993, Sackett et al 2000).

Therefore, the evidence presented in the included studies was assessed and classified using the dimensions of evidence defined by the NHMRC (NHMRC 2000).

These dimensions (Table 9) consider important aspects of the evidence supporting a particular intervention and include three domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 9 Evidence dimensions

Dimensions	Definition
Strength of the evidence	
- Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
- Quality	The methods used by investigators to minimise bias within a study design
- Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 10

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The level of evidence is a measure of the susceptibility to bias of various study designs. Level I evidence implies a study design that is least susceptible to bias, while Level IV evidence implies a study design that is most susceptible to bias. The designations of the levels of evidence are shown in Table 10.

Studies meeting inclusion criteria were assigned a level of evidence as an indication of the susceptibility to bias inherent in particular study designs and were critically appraised to assess their internal validity (or bias), to give an indication of the quality of evidence. Methods of critical appraisal were determined by the study design.

Table 10 Designations of levels of evidence

Levels of evidence[a]	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

[a] Modified from NHMRC (2000)

Critical appraisal of primary research studies

The NHS Centre for Reviews and Dissemination (2001) in the UK has assembled a list of criteria that can be used to evaluate the validity of evidence from various study designs. The relevant validity criteria used in this review for assessing quality of evidence are listed in Table 11.

Table 11 Validity criteria for case-control studies

Study design	Validity criteria[a]
Primary studies	
Crossover study	Randomised method Allocation concealment Blinding of patients, investigators and outcome assessors Proportion lost to follow-up Intention-to-treat analysis Appropriate statistical analysis
Case-control	Explicit definition of cases Adequate details of selection of controls Comparable groups with respect to confounding factors Interventions and other exposures assessed in same way for cases and controls Possibility of over-matching ie cases and controls matched according to factors related to exposure Appropriate statistical analysis

[a] Modified from NHS Centre for Reviews and Dissemination (2001)

Data extraction

Data were extracted from included studies using standardised instruments created for the assessment. Two reviewers examined each article and any discrepancies in evaluation were discussed and resolved through consensus.

Statistical analyses

Where studies did not report statistical analyses examining differences in outcome measures between treatment groups, the absolute risk differences and 95% confidence intervals (CIs) around these differences were calculated. The absolute risk difference describes the absolute change in risk that is attributable to the experimental intervention.

If the effect of an experimental intervention is not statistically significantly different from the effect of a control, the 95% CI will incorporate zero.

The absolute risk differences and 95% CIs were calculated as follows (Altman et al 2000):

Difference: mean outcome of one treatment – mean outcome of other treatment

95% CI:

$$D - \sqrt{(\bar{x}_1 - l_1)^2 + (u_2 - \bar{x}_2)^2} \quad \text{to} \quad D + \sqrt{(\bar{x}_2 - l_2)^2 + (u_1 - \bar{x}_1)^2}$$

D = *difference*

$\bar{x}$ = *mean*

l = *lower confidence interval*

u = *upper confidence interval*

Results of assessment

Search results

The search strategy identified 642 articles. Eleven articles were ordered for full text assessment after review of the abstracts. Of the 11, four met the inclusion criteria and were included in the review. One double-blind crossover study assessing a total of 10 individuals with PD was identified. Due to the small number of participants in this study, three case-control studies were also included.

Another three case-control studies were excluded as the controls were normal, healthy individuals. Other studies were excluded due to results not being presented separately for individuals undergoing DBS (n=1), results being a comparison of those who stopped or continued medication for a group in which all patients underwent DBS (n=1) and results (of a systematic review of case series) referring only to bilateral STN DBS. One study was unavailable to information services at the time of writing.

Is it safe?

Although DBS is non-ablative and is minimally invasive, the procedure may give rise to complications and side effects, some of which are neither reversible nor adaptable. The complications from DBS can arise before surgery, during surgery and in the immediate post-operative period, and after surgery.

Data available on adverse events were derived from case series. Findings from these studies indicated the risk associated with DBS but did not allow quantitation of those risks compared with SMT.

Complications during surgery

Complications during surgery include misplacement, dislocation and fracture of the electrodes, erosion of the skin, formation of seroma in the subcutaneous pocket that receives the IPG, haemorrhage and infection.

Nine case series including 244 participants reported adverse events that occurred during surgery (Table 12). They were commonly related to the implantation of hardware. Intraoperative ischaemic stroke was reported in 1/25 study participants (4.0%) in Anderson et al (2005). Haemorrhages were reported in five studies (Herzog et al 2005, Iansek et al 2002, Krause et al 2004, Loher et al 2002, Romito et al 2003) and occurred at a rate of between 1/48 (2.1%) in Herzog et al (2005) and 1/14 (7.1%) participants in Iansek et al (2002).

Haematomas were reported in a total of five participants across three studies (Anderson et al 2005, Herzog et al 2005, Loher et al 2002) at rates ranging from 1/48 (2.1%) in Herzog et al (2005) to 3/25 (12%) in Anderson et al (2005). Two studies reported confusion at rates of 5/72 (6.9%, Pahwa et al 2003) to 3/14 (21.4%, Iansek et al 2002).

Electrode repositioning/misplacement of electrodes/lead migration were reported in three studies (Iansek et al 2002, Loher et al 2002, Romito et al 2003) and occurred at rates ranging from 2/33 (6.1%) in Romito et al (2003) to 2/14 (14.3 %) in Iansek et al (2002). Romito et al (2002) reported that 8/33 study participants (21.2%) experienced transient intraoperative psychosis and Kitagawa et al (2005) reported that all eight participants in their study experienced slight hand paresthaesia.

Table 12 Complications during surgery and in the immediate post-operative period

Study	Study design	Sample size	Length of follow-up	Adverse event	Patient outcome
Anderson et al (2005)	Case series	25	3, 6 & 12 months	Intraoperative ischaemic stroke (n=1); infraclavicular haematomas (n=3)	Irreversible: Ischaemic stroke resulted in persisting neurological deficits Reversible: Infraclavicular haematomas resolved without intervention
Bejjani et al (2002)	Case report	1	NA	Aggressive behaviour (sudden onset): Occurred within a few seconds when test stimulation conducted at 140 Hz, 60 μsec, 2 V applied at a level 2 mm below the AC-PC. Stimulation immediately stopped and 50 mg propofol injected IV. Episode lasted 5 mins	Reversible: Adjustment of stimulation (3.2 V, 60 μsec, 130 Hz on each side). On waking no recurrence of aggression exhibited
Herzog et al (2003b)	Case series	48	6, 12 & 24 months	Intraoperative subdural haematoma (n=1); minor intracerebral bleeding at side of trajectory lead (n=1)	Not stated
Iansek et al (2002)	Case series	14	6 months	Surgical complications: Confusion (n=3); scalp CSF leak (n=1); intracerebral haemorrhage (n=1); residual cognitive & speech deficits (n=1); electrode repositioning (n=2); inaccurate target (n=1)	Not stated
Kitagawa et al (2005)	Case series	8	6 months	Slight hand paresthaesia following activation of stimulator (n=8); blurred vision caused by ZI/PRL stimulation with a stimulation amplitude of more than 3 V (n=1); hemispastic gait with higher stimulation amplitude of more than 3 V (n=2);	Reversible: Slight hand paresthaesia disappeared in several seconds, other adverse events resolved following adjustment of stimulation parameters
Krause et al (2004)	Case series	27	30 months	Intraventricular haemorrhage (n=1)	Reversible: Adverse event reversed via temporary external ventriculostomy
Loher et al (2002)	Case series	16	1 week, 3 & 12 months	Small pallidal haematoma confined to the GPi (n=1), subcutaneous haemorrhage (n=1), misplacement of electrodes (n=1)	Reversible: All adverse events were reversed
Pahwa et al (2003)	Case series	72	3, 12 & 24 months	Seizures (n=3); confusion (n=5), visual disturbances (n=1), hemiballismus (n=1)	Reversible: All adverse events resolved themselves
Romito et al (2003)	Case series	33	1, 3, 6, 12, 18, 24 & 36 months	Transient intraoperative psychosis (n=7); lead migration (n=2); subarachnoid haemorrhage (n=1)	Not stated

Abbreviations: NA, not applicable; AC-PC, anterior commisure – posterior commisure; ZI/PRL, zona incerta/prelemniscal radiation

After surgery complications

After surgery complications include hardware-, environment- and stimulation- and target-related side effects and complications. A total of 39 case series, including 791 participants, outlined complications that arose after surgery (Table 13). In most cases the adverse events were a combination of both hardware-related and stimulation/target-related complications.

Hardware-related complications

Hardware-related complications including infection, skin erosion, electrode fracture, electrode dislocation and hardware failure can occur at any time after surgery. They are all reversible by explantation of the system or parts of it and re-implantation of a new one (Hariz et al 2002). The additional surgery may need to be performed on an emergency or semi-emergency basis, depending on the patient's response to the sudden re-emergence of symptoms (Hariz et al 2002). A review of existing studies indicated that re-implantation of new hardware devices usually takes place within six months of the initial surgery.

Nine studies (Anderson et al 2005, Constantoyannis et al 2005, Esselink et al 2004, Kleiner-Fisman et al 2004, Krauss et al 2003, Lyons et al 2002, Pahwa et al 2003, Smeding et al 2005, Varma et al 2003) reported electrode or lead problems experienced by participants. The problems ranged from 2/141 participants (1.4%, Constantoyannis et al 2005) to 6/13 participants (46.0%, Lyons et al 2002). Battery depletion and malfunctions were reported in five studies (Chou et al 2004, Lyons et al 2002, Pahwa et al 2003, Rodriguez-Oroz et al 2004, Romito et al 2003) and ranged in incidence from 4/33 participants (12.1%, Romito et al 2003) to 11/13 participants (84.6%, Lyons et al 2002). Rodriguez-Oroz et al (2004) reported that 19 batteries wore out and required replacement after a mean post-operative period of 46 months.

Environment-related complications

Complications may arise due to external interferences such as those caused by magnetic devices and stimulators being inadvertently turned off by dentistry tools (Hariz et al 2002). Many complications arising from external interference can be avoided though the use of a magnetically shielded neurostimulator (Hariz et al 2002).

Stimulation- and target-related complications

Complications or side effects related to the stimulated target and its vicinity are the most frequently reported problems in patients. Many of these effects may be adjustable or reversible, but this is often at the cost of decreased efficacy of stimulation on the symptoms when the previously effective electrical parameters are altered or the stimulator is turned off (Hariz et al 2002).

Table 13 Complications after surgery

Study	Study design	Sample size	Length of follow-up	Adverse event (n)	Patient outcome
Anderson et al (2005)	Case series	25	3, 6 & 12 months	Extracranial lead fracture (n=1), mild delirium (n=3), transient anxiety (n=2), hallucinations (n=1), cognitive changes including short-term memory deficits/difficulty concentrating/apathetic mood (n=2), increased parkinsonian symptoms (n=1)	Reversible: Lead fracture resolved by replacement of lead, mild delirium/anxiety/hallucinations resolved with reduction levodopa Irreversible: Cognitive changes & increased parkinsonian symptoms
Barichella et al (2003)	Case series	32	3 & 12 months	Weight gain (n=29). Mean increase 14.8±9.8% initial body weight. Mean BMI increased to 24.7±3.7 kg/m^2 from 21.6±3.0 kg/m^2	Irreversible
Berney et al (2002)	Case series	24	1, 3 & 6 months	Mood state worsening in moderate to severe depressive range (n=6), transiently suicidal (n=3)	Reversible: Antidepressant treatment administered
Chen et al (2003)	Case series	7	6 months	Stimulation-related ballism/chorea (n=3), blepharospasms (n=5) when using stimulation 3.5 V, transient confusion and agitation (n=3), hypomania (n=2), increased weight (n=7)	Reversible: All adverse events resolved either spontaneously or by adjustment of stimulation parameters
Chen et al (2004)	Case report	1	7 month	Delusion	Reversible: Adverse event resolved by surgical revision
Chou et al (2004)	Case report	2	2 & 3 years	Unilateral IPG battery depletion (n=2), participants exhibited severe rigidity and inability to walk independently	Reversible: Function restored upon replacement of depleted battery
Constantoyannis et al (2005)	Case series	141	24 months	Incisional infection at site scalp (n=7), incisional infection at site chest (n=2), fracture of electrodes (n=2), skin erosion over lead extension connector site (n=2)	Reversible: Infection resolved with suitable antibiotic therapy (n=3) or hardware removal (n=6); fracture of electrodes resolved via replacement (n=2); skin erosion resolved via removal of lead (n=2)
Daniele et al (2003)	Case series	20	3, 6, 12 & 18 months	Psychic akinesia (n=1), mild worsening of dysarthria (n=2), mild worsening of hypophonia (n=1), transient manic symptoms with hypersexuality (n=3), paraesthesia (n=1), paraesthesia & diplopia (n=2), mild subarachnoid haemorrhage (n=1)	Not stated
Doshi et al (2002)	Case series	31	12 months	Depressive symptoms (n=3), suicidal tendencies and attempt (n=1)	Reversible: Antidepressant treatment administered
Esselink et al (2004)	Case series	20	6 months	Severe fluctuating cognitive, behavioural & mood disorders (n=1), transient confusion (n=1), tight extension lead in the neck (n=1), electrode displacement (n=2), CSF leakage (n=1), mild emotional lability (n=6)	Reversible: Transient confusion resolved spontaneously (n=1) Irreversible: All other adverse events

Table 13 (cont'd) Complications after surgery

Study	Study design	Sample size	Length of follow-up	Adverse event (n)	Patient outcome
Funkiewiez et al (2004)	Case series	77	3, 12 & 36 months	Cognitive impairments (n=2), suicide attempts (n=4), hypomania (n=5), impulsive aggressive behaviour (n=2), psychosis (n=4), severe depression (n=1)	Reversible: Hypomania spontaneous recovery (n=4) Irreversible: All other adverse events. Participants with severe depression & psychosis required hospitalisation
Germano et al (2004)	Case series	12	3 days, 12 months	No surgical or peri-operative adverse events observed	NA
Herzog et al (2003a)	Case report	1	1 week, 3 years	Severe hyperactivity, mania, emotionally labile, inability to concentrate	Reversible: Reduced clozapine to 25 mg combined with carbamazepine to address mood disorders
Herzog et al (2003b)	Case series	48	6, 12 & 24 months	Dislocation of impulse generator from site of implantation (n=2), transient psychiatric symptoms (n=11), depression (n=5), manic psychosis (n=1), dysarthria (n=2), apraxia of eyelid opening (n=3), disabling dyskinesias (n=2)	Reversible: Dislocation of IPG from site of implantation resolved by surgical revision and fixation of generator to chest wall, transient psychiatric symptoms improved without specific therapy, depression related symptoms treated with antidepressant medication or adjustment of dopaminergic therapy Irreversible: Dysarthria, disabling dyskinesias and apraxia of eyelid opening
Iansek et al (2002)	Case series	14	6 months	Transient dysarthria (n=1), ataxia (n=1), diplopia (n=1), emotional lability (n=1), leg dysaesthesia (n=1)	Reversible: Transient dysarthria, diplopia, emotional lability Irreversible: Leg dysaesthesia, ataxia
Kleiner-Fisman et al (2004)	Case series	6	Not reported	Scalp cellulitis (n=1), lead erosion (n=1), electrode migration (n=1)	Reversible: All adverse events resolved by replacement of hardware or repositioning
Krack et al (2003)	Case series	49	1, 3 & 5 years	Mortality (n=3), transient delirium (n=12), infection (n=1), seizures (n=2), stimulator repositioning (n=1),dysarthria (n=4), disabling dyskinesia (n=7), impulsive aggressive behaviour (n=1), eyelid opening apraxia (n=8), weight gain (n=39), depression (n=7), hallucinations (n=5), psychosis (n=1), dementia (n=3), apathy (n=7)	Reversible: All adverse events were resolved apart from those listed as irreversible Irreversible: Weight gain (n=39), hallucinations (n=3), dementia (n=3), apathy (n=5), dysarthria (n=2), disabling dyskinesia (n=2), eyelid opening apraxia (n=8)

Table 13 (cont'd) Complications after surgery

Study	Study design	Sample size	Length of follow-up	Adverse event (n)	Patient outcome
Krause et al (2004)	Case series	27	30 months	Worsening of dysphagia (n=1), development of mild dysphagia (n=2), transient hyperhidrosis within minutes of turning on IPG (n=6), lasting hyperkinesias (n=2), increase in falling (n=4), increased libido (n=1)	Reversible: Transient hyperhidrosis resolved spontaneously, increased libido treated with antiandrogens Irreversible: All other adverse events
Krauss et al (2003)	Case series	6	3, 12 & 24 months	Perioral tightness (n=4), dizziness (n=1), weight gain (n=2), lead fracture (n=1), increased dystonia resulting from IPG switching off spontaneously (n=1)	Reversible: Periorial tightness, lead fracture, increased dystonia and dizziness reversed by adjustment of stimulation settings or replacement of leads Irreversible: Weight gain
Kulisevsky et al (2002)	Case series	15	48 hours	Manic syndrome (n=1), euphoria (n=1), increased libido (n=1), hyperactivity (n=1)	Reversible: All adverse events resolved following adjustment of stimulation parameters
Lyons et al (2002)	Case series	13	6,12,18 & 24 months	Paraesthesia (n=7), dysarthria (n=6), disequilibrium (n=3), visual disturbances (n=2) IPG/extension infection (n=1), malfunction of leads (n=4), lead fracture (n=2), battery depletion (n=11)	Reversible: All adverse events were resolved following adjustment of stimulation parameters or removal/replacement of devices
Molinuevo et al (2003)	Case series	15	6 months	Transient confusion/disorientation/abulia (n=2), mild depression (n=1), dysarthria (n=2), hypophonia (n=2)	Irreversible: Mild depression, dysarthria and hypophonia remained 6 months after surgery
Morrison et al (2004)	Case series	17	3 months	Mild cognitive decline, mild decline in attention and language areas	Not stated
Pahwa et al (2003)	Case series	72	3, 12 & 24 months	Dysarthria (n=10), gait abnormality (n=3), paresthaesia (n=2), depression (n=1), muscle spasm (n=1) Malfunction of leads (n=10), incorrect positioning of leads (n=1), intermittent stimulation (n=1), lead fracture (n=2), infection (n=3), skin erosion at site (n=1), battery depletion (n=3), battery malfunction (n=6)	Reversible: All adverse events were resolved following adjustment of stimulation parameters or removal/replacement of devices
Patel et al (2003)	Case series	16	Not reported	No procedure or device related adverse events Stimulation-related complications: Hypophonia (n=3), eyelid apraxia (n=2)	Not stated

Table 13 (cont'd) Complications after surgery

Study	Study design	Sample size	Length of follow-up	Adverse event (n)	Patient outcome
Rodriguez-Oroz et al (2004)	Case series	10	3, 6, 12 & 48 months	Dementia (n=1), hallucinations (n=1), social misconduct (n=1), cognitive impairment (n=2), depression (n=1), severe dysarthria (n=1), subcutaneous erosion and infection (n=1), battery depletion (n=19)	Reversible: Resolved by surgical revisions, adjustment of stimulation parameters, or removal/replacement of devices
Romito et al (2003)	Case series	33	1, 3, 6, 12, 18, 24 & 36 months	Transient: Increased libido (n=4), manic psychosis (n=2), seizure (n=1) Long-lasting: Hypophonia (n=12), dysarthria (n=5), eyelid opening apraxia (n=4), depression (n=3), psychic akinesia (n=2), limb dystonia (n=1), bilateral buccinator spasm (n=1), weight gain (n=33) Stimulation-dependent: Paraesthesias (n=10), ballic-choreic dyskinesias (n=3), blepharospasm (n=2), diplopia (n=2), monolateral buccinator spasm (n=1) Device failure: Unexplained switching off (n=3), sudden end to battery life (n=4)	Reversible: All transient, stimulation-dependent and device failure adverse events Irreversible: Hypophonia, dysarthria, eyelid opening apraxia, depression, psychic akinesia, limb dystonia, bilateral buccinator spasm, weight gain
Rousseaux et al (2004)	Case series	7	3 months	Dysarthria (n=4), worsening of dysarthria (n=2)	Not stated
Sauleau et al (2005)	Case series	17	Not reported	Oculomotor disorders (n=95 contacts), autonomic disorders (n=59 contacts), dystonic disorders (n=32 contacts), sensory disorders (n=20 contacts)	Not stated
Sensi et al (2004)	Case report	1	6 months	Aggressive behaviour, kleptomania	Reversible: Adverse events resolved following administration of antipsychotic drug administration
Simuni et al (2002)	Case series	12	3, 6 & 12 months	Mortality (n=1), chronic subdural haematoma (n=1), subcortical haemorrhage (n=1), seizure (n=1), infection at battery site (n=1), transient change in mental status (n=1)	Reversible: Adverse events resolved by surgical revisions, adjustment of stimulation parameters or removal/replacement of devices

Table 13 (cont'd) Complications after surgery

Study	Study design	Sample size	Length of follow-up	Adverse event (n)	Patient outcome
Smeding et al (2005)	Case series	20	6 & 12 months	Severe confusion (n=1), cognitive decline (n=1), displaced electrodes (n=1)	Reversible: All adverse events resolved by adjustment of electrode positioning
Tamma et al (2002)	Case series	12	3 months	Most common adverse events: Pyramidal, sensorial, oculomotor & vegetative Unspecific events: Chest constriction, malaise, dizziness	Not stated
Tamma et al (2003)	Case series	30	3 & 12 months	Mild confused state (n=9), eye opening apraxia (n=1), weight gain (n=30)	Not stated
Thobois et al (2002)	Case series	18	6 & 12 months	Worsening of dysarthria and freezing (n=1), increased sialorrhoea and drooling (n=1), postural imbalance (n=1), dyskinesias (n=18), mild depression (n=5)	Reversible: Dyskinesia resolved following adjustment of stimulation parameters, depression (n=5) improved spontaneously or after a serotonin reuptake inhibitor treatment
Varma et al (2003)	Case series	7	Not reported	No significant mental effects Lead fracture (n=1), uninhibited behaviour (n=1), visual hallucinations (n=2), transient paraesthesia (n=unspecified)	Reversible: All adverse events were resolved either spontaneously, by surgical revisions, or by medications (levodopa for uninhibited behaviour & quetiapine for visual hallucinations)
Vesper et al (2002)	Case series	84	6 months	Subcutaneous infections in stimulator pocket (n=2), confusion (n=10)	Reversible: Subcutaneous infections were resolved by removal/replacement of devices. Confusions resolved either spontaneously (n=4) or with drug treatments (n=4) Irreversible: Confusion was not resolved by drug treatment or by adjustments of stimulator (n=2)
Vesper et al (2004)	Case series	113	3, 6 & 12 months	Transient disorientation (n=6), infection (n=5), intracerebral haemorrhage (n=2)	Reversible: Transient disorientation resolved spontaneously for 4 patients and 2 patients required antipsychotic medication. Infection resolved by removal/replacement of devices Irreversible: Intracerebral haemorrhage
Visser-Vandewalle et al (2004)	Case series	20	3 & 48 months	Hypomania to mania (n=4)	Not stated

Thalamic DBS-induced side effects can include paraesthesias, muscle cramp, dystonia, dizziness, dysarthria, gait and balance disturbances, limb ataxia, impaired proprioception and decreased fine motor movement. In pallidal DBS, side effects can include confusion, depression, increase in akinesia and induction of gait or speech disturbances. In STN DBS, side effects can include increased dyskinesias, blepharospasm/eyelid-opening apraxia, confusion/memory disturbances, personality changes, mood changes, apathy, cognitive changes, dysphonia/dysarthria and weight gain.

Three studies (Chen et al 2003, Patel et al 2003, Romito et al 2003) specifically reported stimulation-dependent adverse events. These included ballism/chorea, blepharospasm, eyelid apraxia, weight gain and hypophonia.

Other adverse events reported in the case series included:

- infection reported in four studies (Constantoyannis et al 2005, Pahwa et al 2003, Simuni et al 2002, Vesper et al 2004) with an incidence ranging from 3/72 participants (4.2%, Pahwa et al 2003) to 1/12 participants (8.3%, Simuni et al 2002);

- suicidal tendencies and attempts reported in three studies (Berney et al 2002, Doshi et al 2002, Funkiewiez et al 2004) with an incidence ranging from 1/31 participants (3.2%, Doshi et al 2002) to 3/24 participants (12.5%, Berney et al 2002);

- depression reported in nine studies (Berney et al 2002, Doshi et al 2002, Funkiewiez et al 2004, Herzog et al 2003, Molinuevo et al 2003, Pahwa et al 2003, Rodriguez-Oroz et al 2004, Romito et al 2003, Thobois et al 2002) with an incidence ranging from 1/77 participants (1.3%, Funkiewiez et al 2004) to 5/18 participants (27.8%, Thobois et al 2002);

- mortality reported in two studies with an incidence of 3/49 participants (6.1%, Krack et al 2003) and 1/12 participants (8.3%, Simuni et al 2002). It is unclear whether the deaths were related to the procedure or subsequent use of the stimulator.

Thirteen studies reported irreversible adverse events including:

- cognitive changes and increased parkinsonian symptoms in 1/25 participants (4.0%) in Anderson et al (2005);

- weight gain in 29/33 participants (87.9%) in Barichella et al (2003) and 2/6 participants (33.3%) in Krauss et al (2003);

- fluctuating cognitive, behavioural and mood disorders in 1/20 participants (5.0%) in Esselink et al (2004);

- psychosis and severe depression in 5/77 participants (6.5%) in Funkiewiez et al (2004);

- dysarthria in two (4.2%), disabling dyskinesias in two (4.2%) and apraxia of eyelid opening in three (6.3%) of 48 participants in Herzog et al (2003b);

- leg dysaesthesia in 1 (7.1%) and ataxia in 1 (7.1%) of 14 participants in Iansek et al (2002);
- hallucinations in five (10.2%), dementia in three (6.1%) and apathy in seven (14.3%) of 49 participants in Krack et al (2003);
- worsening or development of dysphagia in 3/27 participants (11.1%) in Krause et al (2004);
- depression in 1/15 participants (6.7%) in Molinuevo et al (2003);
- hypophonia in 12 (36.4%) and limb dystonia in one (3.0%) of 33 participants in Romito et al (2003);
- confusion in 10/84 participants (11.9%) in Vesper et al (2002);
- intracerebral haemorrhage in 2/113 participants (1.8%) in Vesper et al (2004).

Not all of these irreversible adverse events, for example weight gain, would require treatment to be stopped. In fact, expert opinion suggests that weight gain may be a desirable outcome since weight loss is common in advanced PD. In addition, the reported adverse events may be reversible upon cessation of stimulation.

Regarding safety of the procedure, the five Australian studies (Appendix E) reported that complications occurred as a result of the surgical procedure for STN DBS and also as a consequence of the stimulation. In summary:

- three of the five studies reported a need to reposition the electrodes in some patients;
- one study reported that some patients had developed infection to either the pacemaker box or the extension wires going towards the brain (the pacemaker box or extension wires had to be removed and were replaced after complete recovery from the infection);
- some patients experienced confusion as a result of surgery;
- two cases of urinary tract infection were considered to be minor complications of surgery.

For major complications relating to surgery:

- two cases of cerebral haemorrhage were reported, one leaving the patient with significant cognitive sequelae necessitating supervised care and the other resulting in death from intracerebral haemorrhage three weeks after the procedure.

In relation to complications associated with stimulation:

- several incidents were reported of patients experiencing dysarthria and hypophonia and, to a lesser degree, emotional lability; and

- two patients died due to progression of the disease with death occurring post-operatively at six months and five years, respectively. There was one patient death for which the cause of death remains unclear.

Hamani et al (2005) performed a systematic review of case series to assess the safety and effectiveness of bilateral STN DBS for the symptoms of PD in a total of 537 individuals. The authors reported the mortality rate, adverse events related to stimulation, general neurological and surgical complications and hardware-related complications. Mortality occurred at a rate of 0.4 per cent.

The adverse events related to stimulation (and rates of occurrence) were: hypophonia (5.8%), eyelid apraxia (4.6%), increased libido (0.8%), sialorrhea (0.9%) and decreased memory (1.1%). Other stimulation-related adverse events included dystonia, paraesthesias, diplopia, dyskinesias and dysarthria; however these events were not reported in the studies or were underestimated.

The adverse events related to general neurological and surgical complications (and rates of occurrence) were: depression (4.7%), mania/hypomania (2.0%), peri-operative confusion (13.7%), cerebrospinal fluid leak (0.1%), meningitis (0.1%), venous phlebitis (0.7%), pneumonia (0.4%), urinary tract infections (0.3%), pulmonary embolism (0.5%), seizures (0.9%), haemorrhage (2.8%). Weight gain was also considered to fall into this category, but was reported to be under-quantified in the studies (Hamani et al 2005).

The adverse events from hardware-related complications (and rates of occurrence) were: lead problems including lead migration, breakage and repositioning (4.5%), infections of the hardware (3.4%), swelling in the region of the IPG/extension cables (0.8%) and battery failure (0.4%).

Summary of the safety of DBS for the symptoms of PD

Conclusions regarding the safety of DBS for the treatment of symptoms of PD were similar for the current review and the identified systematic review. Some adverse events were reported to be transient or resolved with treatment, but a number were reported to be irreversible. The assessment of the safety of DBS for the treatment of symptoms of PD is limited by:

- follow-up of the hardware to a maximum of only 60 months in participants included in each of the studies; and

- the lack of data assessing the comparative safety of DBS and SMT.

Expert opinion suggests that DBS, which is potentially reversible, is as safe as, and possibly safer than, irreversible ablative surgery. Complications arising from DBS are more likely to be hardware-related rather neurologic.

Is it effective?

No RCTs were identified that compared the effectiveness of DBS for the treatment of symptoms of PD with placebo or SMT.

The assessment of the effectiveness of DBS for PD was completed by the critical appraisal of one double-blind crossover evaluation and three case-control studies. All patients in the double-blind crossover study had the DBS device implanted and symptoms were evaluated with the device turned OFF or turned ON. In the case-control studies, cases were participants with PD who received DBS and controls were participants with PD whose symptoms were managed by SMT.

The double-blind crossover study by Rodriguez-Oroz et al (2004) included 10 participants.

The case-control study of Capecci et al (2005) included 23 case and 16 control subjects. All participants were eligible for DBS, however most controls chose not to have the device implanted because of fear of surgery. Four controls later changed their minds and underwent surgery 13, 14, 16 and 17 months after enrolment in the study. They are included in the data from the 12-month follow-up, which was available for all participants. Twenty-four-month follow-up was available for only 13 cases and eight controls.

The study of Hjort et al (2004) included 10 cases and 10 controls and that of Just & Ostergaard (2002) included 11 cases and 13 controls. The controls in each were individuals with PD admitted to a waiting list for DBS surgery.

Critical appraisal of the double-blind crossover and case-control studies

The descriptive characteristics of the double-blind crossover study and three case-control studies identified from a systematic search of the literature and meeting the *a priori* inclusion criteria are listed in Table 14. The double-blind crossover study by Rodriguez-Oroz et al (2004) was conducted in Spain and the enrolled participants had a mean age of 62 years (range 53–73) when surgery was performed and a maximum follow-up of 48 months post-surgery. Participants in the double-blind crossover study underwent surgery between 1996 and 1999 and the assessment was performed between 2001 and 2003.

Of the case-control studies, one was conducted in Italy and two were conducted in Denmark. The minimum and maximum lengths of follow-up were three months (Hjort et al 2004) and 24 months (Capecci et al 2005), respectively. The study populations varied in size from 20 (Hjort et al 2004) to 39 (Capecci et al 2005). The majority of participants in Hjort et al (2004) and Just & Ostergaard (2002) were male. The mean or median age of the participants was similar between studies. The mean duration of PD varied from 10.3 years in the control participants in Capecci et al (2005) to 17.7 years in the case participants in Hjort et al (2004).

Table 14 Descriptive characteristics of double-blind crossover and case-control studies

Study	Location	Enrolment period	Maximum length of follow-up (months)	Study population			
				Sample size	№ male (%)	Mean age (years±SD)	Mean duration of PD (years±SD)
Double-blind crossover study							
Rodriguez-Oroz et al (2004)	Spain	Patients operated on between 1996 and 1999, evaluated between 2001 and 2003	48	10	8 (80.0)	At time of surgery: 62 Range: 53–73	Not reported
Case-control studies							
Capecci et al (2005)	Italy	Jul 2000–Jul 2002	24	All: 39 Cases: 23 Controls: 16	All: 18 (46.2) Cases: 12 (52.2) Controls: 6 (37.5)	Cases: 59.5±7.5 Controls: 62.2±6.5	Cases: 12.8±4.2 Controls: 10.3±4.2
Hjort et al (2004)	Denmark	Not reported. (Surgeries performed between Feb and Jun 2002)	4 (3 months post surgery)	All: 20 Cases: 10 Controls: 10	All: 12 (60.0) Cases: 5 (50.0) Controls: 7 (70.0)	Cases: 60.1 Range: 52–71 Controls: 58.5 Range: 41–69	Cases: 17.7 Range: 10–28 Controls: 13.2 Range: 5–20
Just & Ostergaard (2002)	Denmark	Not reported. (Surgeries performed between Feb and Sep 2000)	6	All: 24 Cases: 11 Controls: 13	All: 15 (62.5) Cases: 8 (72.7) Controls: 7 (53.8)	Cases: 59.8±6.8 Controls: 61.4±5.7	Cases: 14.0±6.0 Range: 7–25 Controls: 16.0±6.0 Range: 10–27

Table 15 summarises the inclusion and exclusion criteria used to recruit participants in the four studies. Cappeci et al (2005) reported explicit inclusion criteria and Rodriguez-Oroz et al (2004) described the enrolled participants. Hjort et al (2004) and Just & Ostergaard (2002) reported no inclusion criteria.

Table 15 Selection criteria for double-blind crossover and case-control studies

Study	Inclusion	Exclusion
Double-blind crossover study		
Rodriguez-Oroz et al (2004)	A consecutive series of patients regularly assessed at the centre ie patients were not selected on the basis of having experienced an especially good response to DBS (positive bias)	Not reported
Case-control studies		
Capecci et al (2005)	• Participants were eligible for the study if they met the internationally agreed criteria for DBS • Patients with advanced PD who displayed clinical fluctuations or side effects from drug therapy leading to moderate to severe disability and were no longer having significant advantages from adjustments to drug scheduling • Participants who met the requirements of the Core Assessment Program for Surgical Intervention Therapies (CAPSIT) in PD and gave informed consent to the operation were considered cases and those deciding against surgery acted as controls	Not reported
Hjort et al (2004)	Participants were described as patients with advanced PD and motor complications	Not reported
Just & Ostergaard (2002)	Case participants were described as having advanced idiopathic PD. Control participants were described as a "similar group of patients"	Not reported

Validity of double-blind crossover and case-control studies

The study by Rodriguez-Oroz et al (2004) met most of the validity criteria for a double-blind crossover. Although the study did not report the method of randomisation of participants, the authors explicitly reported concealment of randomisation and blinding of participants, investigators and outcome assessors. Analyses were performed using the entire study population as there were no losses to follow-up due to the relatively short duration of the double-blind crossover part of the study.

The validity characteristics of the three case-control studies are summarised in Table 16. Only the study by Capecci et al (2005) explicitly defined the case participants, reporting that all participants had median Hoehn & Yahr stage IV disease. One study (Hjort et al 2004) did not report disease severity in the cases or controls beyond duration of disease. All of the studies assessed the interventions the same way for cases and controls and showed no evidence of overmatching the cases and controls for confounding factors.

Table 16 Validity characteristics of the case-control studies

Study	Design NHMRC Level of Evidence	Explicit definition of cases?	Comparable groups with respect to confounding factors?	Interventions assessed in same way for cases and controls?	Possibility of overmatching?
Capecci et al (2005)	Prospective, non-equivalent pre-test/post-test control group study Level III	Yes	Median Hoehn & Yahr scale Cases: Stage IV Controls: Stage IV	Yes	No
Hjort et al (2004)	Case-control Level III	No – advanced PD with motor complications	Duration of disease in years Cases: Mean: 17.7 Range: 10–28 Controls: Mean: 13.2 Range: 5–20	Yes	No
Just & Ostergaard (2002)	Case-control Level III	No – advanced idiopathic PD	Duration of disease in years: Mean±SD, range Cases: 14±6, 7–25 Controls: 16±6, 10–27 PDQ-39SI: Mean±SD, range Cases: 38.4±11.3, 25.0–63.3 Controls: 41.3±12.1, 25.4–71.1	Yes	No

Table 17 presents the results of the double-blind crossover study by Rodriguez-Oroz et al (2004). Double-blind evaluations were performed only in the OFF medication state in which medication was stopped overnight. The DBS device was switched off at 6am and evaluations were initiated at 9am. Participants were randomly assigned to one of two treatment sequences.

In sequence 1, participants underwent evaluation with the stimulator turned off for an additional two hours and were re-evaluated when the device was switched on for two hours. In participants randomly assigned to sequence 2, this order was reversed. The effect of stimulation was observed regardless of the order in which the device was switched ON and OFF (Table 17). The mean change in UPDRS III scores was from 43 points with stimulation OFF to 26 points with stimulation ON (p=0.04), representing an improvement in motor symptoms with stimulation. The observed improvements were 38 per cent for rigidity, 55 per cent for tremor and 40 per cent for axial symptoms. The walking and tapping tests were also significantly improved with stimulation. Four patients who were unable to walk with stimulation OFF were able to complete the task with stimulation ON. The results of the double-blind crossover study showed that the effects of DBS remain reversible and effective four years after surgery.

Table 17 Results of UPDRS III, walking test and tapping scores in the double-blind crossover study

Assessment	DBS OFF Mean (range)	DBS ON Mean (range)	p value	Change (%)
UPDRS III				
Sequence 1[a] (n=6)	49 (58–66)	30 (13–52)		38.7
Sequence 2[a] (n=4)	31 (27–33)	18 (16–19)		41.9
Mean	43 (27–66)	26 (13–52)	0.04	39.5
Walking test	25 (18–27)	16 (14–20)	0.04	36.0
Tapping	114.2 (23–192)	152.4 (21–223)	0.04	33.4

Source: Rodriguez-Oroz et al (2004).
Abbreviations: UPDRS III, Unified Parkinson's Disease Rating Scale Motor section
[a] Described in the text

Rodriguez-Oroz et al (2004) also reported an open assessment of the motor state undertaken on patients on and off medication (a minimum of 12 hours since the last dose) before and after surgery, and on and off stimulation one and four years after surgery.

Four years after surgery, the UPDRS OFF medication score and the magnitude (OFF-ON difference) of the response to levodopa were reduced by 62 and 77 per cent, respectively, compared with scores before surgery. The levodopa daily dose decreased from 1,287.5 mg (range 300 mg to 2,050 mg) pre-operatively to 641 mg (range 140 mg to 1,140 mg) four years post-operatively.

Four years after surgery, assessment of the UPDRS part II, Activities of Daily Living (ADL) revealed improvement by 61 per cent in the medication OFF state but no significant differences in the medication ON state compared with pre-surgery scores. No significant differences were observed in ADL scores in the ON and OFF medication state at one year post-surgery compared with pre-surgery scores. Global assessment of the motor situation at four years by examiners and patients showed an improvement of 71 per cent and 52 per cent, respectively.

Participants in Capecci et al (2005) were evaluated in "defined-OFF" and "defined-ON" states at baseline and 12 and 24 months (Table 18). Case participants were evaluated following surgery in both the ON stimulation-OFF medication and ON stimulation-ON medication states. The authors reported that there was a statistically significant difference between the treatment groups at both 12 and 24 months in the UPDRS-ADL, UPDRS-ADL disability items, Brown's Disability Scale (B'DS) and the Functional Independence Measure (FIM). The UPDRS-ADL score (mean±SD) for case participants was 16.6±4.1 points at baseline, 8.0±4.6 points at 12 months post-surgery and 10.6±3.3 points at 24 months post-surgery.

The decrease in UPDRS-ADL scores from baseline to 12 and 24 months post-surgery indicated an increased ability for the case participants to complete activities of daily living. In contrast, control participants displayed a gradual increase in UPDRS-ADL scores from 14.4±4.7 points at baseline to 14.9±6.0 points at 12 months and 16.3±7.9 points at 24 months of follow-up. This decreased ability to perform activities of daily living is most likely attributable to a worsening of PD symptoms.

Table 18 Primary outcome measures in cases and controls and results of the two way analyses of variance

Outcome	Cases			Controls			p value[a]	
	Baseline[b] (n=23)	12 months (n=23)	24 months (n=13)	Baseline (n=16)	12 months (n=16)	24 months (n=8)	12 months	24 months
UPDRS-ADL	16.6±4.1	8.0±4.6	10.6±3.3	14.4±4.7	14.9±6.0	16.3±7.9	<0.0001	0.0050
UPDRS-ADL DI	12.5±2.5	6.4±5.2	6.6±4.4	8.6±2.7	8.5±3.1	10.4±4.1	0.0050	<0.0001
B'DS	41.8±23.4	18.3±11.6	19.0±13.5	35.3±15.5	41.9±26.4	42.8±25.6	0.0020	0.0070
FIM	108.2±17.9	117.6±4.8	118.2±4.6	113.6±9.4	106.0±11.5	101.2±16.0	0.0400	0.0400

Source: Capecci et al (2005).

Abbreviations: B'DS, Brown's Disability Scale; FIM, Functional Independence Measure; UPDRS-ADL, Unified Parkinson's Disease Rating Scale for Activity of Daily Living; UPDRS-ADL DI, Unified Parkinson's Disease Rating Scale for Activity of Daily Living Disability Items (composite subtotal of scores from speech, handwriting, cutting food, dressing, hygiene, turning in bed, and gait)

[a] Time x treatment p value calculated by including disability scores as independent variables in a two-way analysis of variance for repeated measures, comparing the functional trends of the two groups of patients and considering time and treatment effects both separately and cumulatively

[b] All outcomes are presented as mean±SD

Capecci et al (2005) reported that there was a statistically significant difference between the treatment groups at both 12 and 24 months in the following outcomes: UPDRS III TIME-OFF, daily OFF rate, rate of dyskinesia, tremor, gait, postural reflex, sensory symptoms and LEDD (Table 19).

The TIME-OFF scores refer to the period during which participants are off SMT. Control participants displayed a gradual increase in UPDRS III TIME-OFF scores (mean±SD) from 37.4±5.1 points at baseline to 39.8±6.3 points at 12 months and 41.7±7.9 points at 24 months of follow-up. For case participants (where TIME-OFF scores were measured with stimulation on), the UPDRS III TIME-OFF score (mean±SD) was 38.3±11.6 points at baseline, 17.9±11.7 points at 12 months following surgery and 18.0±4.7 points at 24 months of follow-up. These results suggest that DBS is effective in maintaining increased motor control in participants, even in the absence of SMT.

Measures of the mean daily OFF rate refer to the period of time per day whilst on medication during which the medication is ineffective and participants are disabled by the symptoms of PD. The mean±SD daily OFF rate for case participants with stimulation ON decreased from 46.1±1.8 per cent at baseline to 5.9±6.4 and 5.2±6.3 per cent at 12 and 24 months, respectively. The authors report that the OFF-period rate decreased by 90 per cent in all 23 case participants with highly significant reductions in the rate of dyskinesia ($p<0.0001$), tremor ($p<0.0001$) and sensory symptoms ($p<0.0001$), whose scores tended to zero in all cases. Significant changes were also observed for axial symptoms such as gait ($p<0.001$), freezing ($p<0.01$) and falls ($p=0.04$), however these scores did not decrease uniformly among the case participants.

In contrast, the daily OFF rates (mean±SD) for control participants was 38.1±15.5 per cent at baseline, increasing to 42.1±4.6 and 45.8±8.9 per cent at 12 and 24 months, respectively. These results indicate that DBS can ameliorate the symptoms of PD by smoothing out motor fluctuations during periods in which SMT is not effective and provide more time during which the symptoms of PD are maintained at levels similar to those when medication is effective.

Capecci et al (2005) also reported that case participants had reduced LEDDs compared with control participants with a 31.4% and 39.2% reduction in LEDD at 12 and 24 months of follow-up, respectively.

Table 19 Trends of secondary outcome measures in cases and controls and results of two-way analysis of variance

Outcome	Cases			Controls			p value[a]	
	Baseline (n=23)	12 months (n=23)	24 months (n=13)	Baseline (n=16)	12 months (n=13)	24 months (n=8)	12 months	24 months
UPDRS III TIME-OFF[b]	38.3±11.6	17.9±11.7	18.0±4.7	37.4±5.1	39.8±6.3	41.7±7.9	<0.0001	0.001
UPDRS III TIME-ON[b]	10.2±8.2	11.7±8.7	13.5±8.5	12.0±9.2	13.0±5.4	14.0±5.8	NS	NS
Daily OFF rate[b]	46.1±1.8	5.9±6.4	5.2±6.3	38.1±15.5	42.1±4.6	45.8±8.9	<0.0001	0.0001
Rate of dyskinesia[c]	2 (1–3)	0 (0–1)	0 (0–1)	1 (1–2)	2 (1–2)	2 (1–3)	<0.0001	0.0100
Drooling[c]	0 (0–1)	0 (0–1)	1 (0–1)	0 (0–1)	0 (0–1)	1 (0–1)	NS	NS
Speech[c]	2 (1–2)	1 (0–2)	2 (1–3)	0 (0–1)	0 (0–1)	1 (0–2)	NS	NS
Tremor[c]	2 (1–3)	0 (0–1)	0 (0–1)	1 (1–2)	1 (1–2)	2 (1–2)	0.0001	0.0010
Gait[c]	2 (1–2)	1 (0–1)	1 (1–2)	1 (1–2)	2 (1–2)	2 (1–2)	0.0100	0.0500
Freezing[c]	2 (0–3)	1 (0–2)	1 (1-2)	1 (1–2)	2 (1–2)	1 (1–2)	0.0400	NS
Postural reflex[c]	2 (1–2)	1 (0–2)	1 (1–2)	1 (0–1)	1 (0–2)	1 (0–2)	0.0070	0.0070
Falls[c]	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–0)	1 (0–1)	0.0500	NS
Sensory symptoms[c]	2 (1–2)	0 (0–0)	0 (0–1)	1 (1–2)	2 (1–3)	2 (1–2)	0.0001	0.0010
LEDD[b]	987.9±427.0	708.0±311.0	561.0±347.0	961.2±474.0	1032.4±356.6	922.5±289.1	0.0005	0.0500
BDI[b]	14.4±6.9	9.5±2.6	9.5±4.1	13.5±6.4	10.5±4.9	8.5±4.9	NS	NS

Source: Capecci et al (2005).

Abbreviations: BDI, Beck Depression Inventory; LEDD, levodopa equivalent daily dose; NS, not significant; UPDRS III, Unified Parkinson's Disease Rating Scale Motor section

[a] Time x treatment p value calculated by including disability scores as independent variables in a two-way analysis of variance for repeated measures, comparing the functional trends of the two groups of patients and considering time and treatment effects both separately and cumulatively

[b] Mean±SD

[c] Median (quartiles)

Hjort et al (2004) reported that cases had a mean UPDRS score OFF medication of 48.8 one month before surgery and of 21.9 three months after surgery ($p<0.002$) and that the Hoehn & Yahr stage off medication decreased from 4.2 before surgery to 2.6 after surgery. The authors did not report the mean UPDRS and Hoehn & Yahr stages for the control group. The LEDD was reduced by 29 per cent from 1,138 mg to 813 mg in cases before and after surgery, respectively. For cases, the number of participants not taking sleep medicine or clozapine increased from five (50%) to eight (80%) after surgery. For controls, the number of participants not taking sleep medicine or clozapine at baseline and at four months of follow-up was seven (70%) and eight (80%), respectively.

In the study of Just & Ostergaard (2002) there was a significant difference in mobility, ADL, stigma, cognition, bodily discomfort and the PDQ-39SI for cases between baseline and six months after surgery (Table 20). No significant differences were observed for any of the subscales or PDQ-39SI for control participants at three or six months of follow-up (Table 20). There were statistically significant differences in mobility, ADL, cognition and PDQ-39SI between the groups at six months of follow-up. The results of the PDQ-39SI scores indicated that DBS significantly improves the QoL for individuals with PD.

Just & Ostergaard (2002) also reported UPDRS II, UPDRS III and Hoehn & Yahr stage scores for case participants OFF and ON medication at baseline, and at three and six months of follow-up. (They did not report these scores for the SMT control group). Statistically significant reductions in the UPDRS II and UPDRS III scores were observed for surgical participants with stimulation on during the OFF medication states at three and six months of follow-up. Participants ON medication showed significant reductions in the UPDRS II scores at six, but not three months of follow-up and significant reductions in UPDRS III scores at both three and six months. The Hoehn & Yahr scores were significantly different only in the OFF medication state, at three and six months of follow-up. In addition, the OFF periods experienced by the surgical participants (mean±SD) decreased from 31.0±19.0 per cent at baseline to 2.9±5.7 per cent at three months ($p=0.001$) and 0.0±0.0 per cent at six months ($p=0.001$).

Table 20 Subscale scores and PDQ-39SI scores at baseline, 3 and 6 months for cases and controls

Outcome	Cases (n=11)					Controls (n=13)					Difference between groups	
	Baseline	3 months	6 months	Change from baseline to 3 months	Change from baseline to 6 months	Baseline	3 months	6 months	Change from baseline to 3 months	Change from baseline to 6 months	Change from baseline to 3 months	Change from baseline to 6 months
	Mean±SD	Mean±SD	Mean±SD	Mean (95% CI)	Mean (95% CI)	Mean±SD	Mean±SD	Mean±SD	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Mobility	61.5±16.2	33.4±16.5	34.7±21.8	28.1 (15.3, 41.0)	26.8 (8.6, 45.1)	65.0±21.4	65.0±20.4	67.5±19.5	0.0 (–6.8, 6.8)	–3.3 (–9.6, 3.1)	28.1 (13.5, 42.6)	30.1 (10.7, 49.4)
ADL	64.3±16.8	36.4±21.4	25.8±15.5	28.0 (15.5, 40.6)	38.6 (26.4, 50.8)	52.9±15.3	54.5±15.1	57.1±15.5	–1.6 (-8.1, 4.9)	–5.0 (–13.6, 3.6)	29.6 (15.4, 43.7)	43.6 (28.7, 58.5)
Emotional well-being	29.9±14.5	19.3±22.5	20.5±18.9	10.6 (–0.8, 22.0)	9.5 (0.3, 18.6)	33.0±16.2	31.7±17.9	34.2±18.0	1.3 (–2.9, 5.4)	0.4 (–4.3, 5.2)	9.3 (–2.8, 21.4)	9.1 (–1.1, 19.5)
Stigma	23.9±16.9	13.1±17.1	8.0±18.4	10.8 (2.4, 19.2)	15.9 (4.4, 27.4)	35.1±24.0	31.7±20.6	33.8±26.5	3.8 (–0.9, 8.6)	4.4 (–4.4, 13.2)	7.0 (–2.6, 16.7)	11.5 (–3.1, 26.0)
Social support	21.6±21.0	17.0±20.6	16.3±25.4	4.5 (–7.0, 16.0)	5.3 (–11.9, 22.5)	17.9±17.6	23.1±27.0	21.7±20.9	–5.1 (–18.5, 8.3)	–3.3 (–18.0, 11.3)	9.6 (–8.1, 27.3)	8.6 (–14.0, 31.2)
Cognition	34.7±25.2	24.4±22.7	19.3±17.3	10.2 (–3.3, 23.8)	15.3 (6.3, 24.4)	37.9±18.6	40.3±18.0	41.9±17.7	–2.4 (–8.5, 3.7)	–2.5 (–7.7, 2.7)	12.6 (–2.3, 27.4)	17.8 (7.3, 28.2)
Communication	31.8±23.8	32.5±25.4	29.5±21.5	–0.8 (–10.6, 9.1)	2.3 (–9.2, 13.8)	42.9±14.0	39.7±16.0	40.8±14.9	3.2 (–0.6, 7.1)	1.7 (–5.1, 8.4)	–4.0 (–14.6, 6.5)	0.6 (–12.8, 13.9)
Bodily discomfort	39.4±26.6	18.9±17.9	24.3±17.3	20.5 (6.0, 34.9)	15.1 (0.8, 29.5)	45.5±21.9	50.0±21.0	45.0±18.9	–4.5 (–13.6, 4.6)	4.2 (–4.8, 13.6)	25.0 (8.0, 42.1)	10.9 (–6.1, 28.0)
PDQ-39SI	38.4±11.3	24.4±15.4	22.3±12.5	14.0 (5.8, 22.2)	16.1 (9.0, 23.1)	41.3±12.1	42.0±12.3	42.7±12.1	–0.7 (–4.5, 3.2)	–0.4 (–5.0, 4.1)	14.7 (5.7, 23.8)	16.5 (8.1, 24.9)

Source: (Just & Ostergaard 2002)
Abbreviations: ADL, Activity of Daily Living; CI, confidence interval; PDQ-39SI, Parkinson's Disease Questionnaire Summary Index

Discussion of double-blind crossover and case-control studies

The results of the effectiveness of DBS for the treatment of PD symptoms were assessed from one double-blind crossover and three case-control studies. Since the UPDRS III scores of individuals with PD are expected to increase by 1.5 to 3.6 points annually (Louis et al 1999), these studies indicated that DBS ameliorated the symptoms of PD as measured by the UPDRS and improved QoL as measured by the PDQ-39SI.

Rodriguez-Oroz et al (2004) reported a mean decrease in UPDRS III scores of 39.5 per cent. Similarly, the case-control study by Capecci et al (2005) reported that UPDRS-ADL scores were reduced at the 12- and 24-month follow-up, representing an improvement in the ability to complete activities of daily living for case participants. The UPDRS III TIME-OFF scores of case participants decreased at 12 and 24 months of follow-up, representing an improvement in motor symptoms. The results also indicated that DBS was effective in maintaining motor function in the absence of SMT (Capecci et al 2005).

Hjort et al (2004) also reported a decrease in the UPDRS III score OFF medication at three months post-operatively. In addition, the decrease in LEDDs ranged from 29 per cent (Hjort et al 2004) to 43.2 per cent (Capecci et al 2005). These results therefore show that DBS can ameliorate the symptoms of PD and reduce the LEDDs required to maintain control of the symptoms of PD.

Two case-control studies (Capecci et al 2005, Hjort et al 2004) also reported significant reductions in the daily OFF rate in which medication is not effective. Capecci et al (2005) reported a reduction in the daily OFF rate from 46.1 per cent at baseline to 5.2 per cent at 24 months of follow-up for participants undergoing DBS, whilst those who continued on SMT showed a slight increase in daily OFF rates between baseline and 24 months of follow-up. Hjort et al (2004) also reported a reduction in the daily OFF rate from 31.0 per cent at baseline to zero per cent at 6-months of follow-up, however this study did not report the daily OFF rate for control participants. These results indicate that DBS can ameliorate the symptoms of PD by smoothing out the motor fluctuations during periods when SMT is ineffective and provide significantly more time during which the symptoms of PD are maintained at levels similar to those when medication is effective.

Most of the studies reported an improvement in UPDRS and PDQ-39SI scores; however the following issues highlight the limitations of the data presented:

- The double-blind crossover study included only 10 participants (for whom the inclusion criteria were not explicit) and the DBS device was turned off for a period of only two hours.
- The results of the studies presented in this assessment may be biased for the following reasons:
  - Two of the case-control studies included in this review stated that case participants were enrolled consecutively, however consecutive enrolment of the control participants was not reported. One case-control study stated that participants were selected from a larger group of individuals, which may introduce selection bias.
  - There may have been selective reporting. One of the three studies explicitly stated that data collection was prospective.

- The length of follow-up in these studies was only 48 months, as a result of which the long-term (>5 years) effectiveness of DBS for the symptoms of PD has not been established.

- Participants in the studies may not be representative of those eligible for DBS in Australia.

Results of a systematic review of bilateral STN DBS (Hamani et al 2005)

Hamani et al (2005) reported the results of a systematic review of the literature that assessed the safety and effectiveness of DBS for the treatment of the symptoms of PD (Table 21). The review included 38 case series from 34 neurosurgical centres in 13 countries. Twenty-two of these were assessed for outcome and an additional 16 were included for motor subscores or adverse events. The results indicate that STN DBS is effective in improving mean UPDRS ADL and Motor scores and in decreasing the LEDDs. Improvements in these scores were observed at six, 12, 24 and 60 months post-surgery for patients OFF and ON medication, compared with results before surgery in the medication-OFF state.

The UPDRS II score (mean±SD) of participants OFF medication was 27.0±6.8 points at baseline, 11.9±5.0 at 12 months post-surgery and 15.6±8.5 points at 60 months. These results indicate that DBS allowed individuals with PD to maintain increased abilities to perform activities of daily living even in the absence of medication. However, the UPDRS II scores of participants ON medication did not change significantly. Scores were 9.7±5.9 points at baseline and 8.3±5.6 and 14.0±7.0 points at 12 and 60 months, respectively.

The UPDRS III score of participants OFF medication was 50.2±20.3 points at baseline, 22.3±12.1 at 12 months and 25.8±21.3 points at 60 months, indicating that even in the absence of medication, DBS allows individuals with PD to maintain increased motor function similar to the levels observed when individuals with PD are on effective medication. However, the UPDRS III scores of participants ON medication did not change significantly from 21.2±9.0 points at baseline to 15.6±7.9 and 21.1±12.5 points at 12 and 60 months, respectively.

At 12 and 60 months after surgery, the LEDDs were reduced by 47.0 per cent and 59.0 per cent, respectively, compared to baseline, indicating the beneficial effects of DBS with regard to motor function and the performance of activities of daily living. This reduction in LEDDs might also reduce significantly some of the side effects associated with prolonged high-dose levodopa treatment.

Table 21 Results from systematic review of bilateral STN DBS

Outcome	Baseline[a]	Time after surgery:			
		6 months[b]	12 months	24 months	60 months[c]
UPDRS II: ADL					
OFF[d]	27.0±6.8 (n=311)	11.4±5.8 (58) (n=142)	11.9±5.0 (56) (n=241))	14.7±6.3 (46) (n=48)	15.6±8.5 (42) (n=42)
ON[e]	9.7±5.9 (64) (n=311)	7.0±6.2 (74) (n=95)	8.3±5.6 (69) (n=209))	11.6±5.3 (57) (n=48)	14.0±7.0 (48) (n=39)
UPDRS III: Motor					
OFF[d]	50.2±20.3 (n=471)	24.9±12.1 (50) (n=209)	22.3±12.1 (56) (n=374)	24.4±10.9 (51) (n=58)	25.8±21.3 (49) (n=42)
ON[e]	21.2±9.0 (58) (n=411)	14.7±9.7 (71) (n=209))	15.6±7.9 (69) (n=374)	17.4±8.0 (65) (n=58)	21.1±12.5 (58) (n=39)
LED	1,264.3±577.9 (n-345)	580.3±389.9 (54) (n=139))	669.7±341.1 (47) (n=222)	530.3±400.0 (58) (n=19)	518.0±333.0 (59) (n=42)

Source: Hamani et al (2005)

Abbreviations: UPDRS, United Parkinson's Disease Rating Scale; LEDD, levodopa-equivalent daily dose

[a] Values represented as mean±SD (% reduction). Percentage reductions are relative to pre-operative off medication scores, except for LEDD, in which the percentages are relative to pre-operative dosage

[b] All post-operative scores are on stimulation

[c] Data obtained from a single centre (Krack et al 2003)

[d] OFF medication

[e] ON medication

Similar results were observed for the UPDRS Motor Subscores of tremor, rigidity, akinesia-bradykinesia, gait and postural instability (Hamani et al 2005).

Hamani et al (2005) also reported UPDRS IV and subscore results. The UPDRS IV score provides information about the complications of therapy, in particular the loss of a smooth and sustained response to medication and occurrence of disabling dyskinesias. For the ON-stimulation, ON-medication state, UPDRS IV scores improved compared with pre-operative ON-medication scores by 73 per cent following six months of treatment with DBS (n=59) and by 94 per cent following 12 months (n=44) (Hamani et al 2005). Dyskinesias improved by 67 and 74 per cent at six and 12 months, respectively, compared with pre-operative ON-medication scores. Dyskinesia subscores for duration, disability and fluctuations consistently showed improvement following surgery and treatment with DBS for up to five years of follow-up (Hamani et al 2005).

Discussion of a systematic review of bilateral STN DBS

The data presented in Hamani et al (2005) indicated that DBS was effective in reducing the symptoms of PD. The results of the systematic review indicated that DBS allowed the maintenance of abilities to perform activities and increased motor function in the absence of effective SMT. The study by Hamani et al (2005) also showed that LEDDs were decreased with STN DBS. In the absence of a comparator group, it is not possible to quantitate the effect attributable to DBS; however, the worsening of akinesia, speech, postural stability, freezing of gait and cognitive function is consistent with the natural history of PD over time (Krack et al 2003).

Summary of the effectiveness of DBS for the symptoms of PD

The effectiveness of DBS for the treatment of symptoms of PD was assessed from one double-blind crossover and three case-control studies. DBS appears to be effective for the treatment of PD symptoms, with statistically significant changes observed between

case and control participants in UPDRS and PDQ-39SI scores. These results therefore show that DBS can ameliorate the symptoms of PD (as measured by the UPDRS ADL and Motor sections) and reduce the LEDDs required to maintain control of the symptoms of PD.

In addition, data from these studies indicated that DBS is effective in maintaining control of the symptoms of PD in the absence of effective SMT. Patients experienced up to a 90 per cent reduction at 24 months following surgery in the daily OFF rate. However, the assessment of the effectiveness of DBS for the treatment of symptoms of PD was limited by:

- the number of individuals analysed;
- significant losses to follow-up in some studies; and
- follow-up of the participants to a maximum of only 48 months.

The data from these studies are, however, supported by those reported in the systematic review of the case series literature that included 38 individual studies and up to 471 participants. The review by Hamani et al (2005) indicated the benefits of DBS in the absence of effective SMT.

In addition, DBS enabled the use of decreased LEDDs. This reduction in LEDD may also significantly reduce some of the side effects of high-dose levodopa treatment over a long time. The results reported in the double-blind crossover and case-control studies also supported the suggestion that beneficial effects for participants in the case series were attributable to DBS.

Data on the safety and effectiveness of DBS from Australian case series (Appendix E) are consistent with those reported in the current review of one double-blind crossover study and three case-control studies and the published systematic review covering the large body of evidence from international case series.

What are the economic considerations?

General framework

The original MSAC assessment report of DBS for the symptoms of PD (MSAC 2001) found that the available evidence was insufficient to allow a definite estimate of the cost-effectiveness of DBS compared to either ablative surgery or SMT as the comparator in the treatment of severe PD. Therefore, an exploratory cost analysis was done using cost data from an HTA report undertaken in the UK for pallidotomy, thalamotomy and DBS for severe PD.

Using the assumption that four follow-up visits per year would be required for stimulator adjustment, it was estimated that the costs for DBS would increase to between $60,917 and $75,808 and that the incremental cost of DBS compared to ablative surgery would be between $25,330 and $51,385. The Applicant provided an estimated cost for the procedure of $26,245, but this was considered to be an underestimation by the evaluator because it covered procedural costs but not follow-up costs, such as programming.

A review of the literature for MSAC (2001) found only one paper with useable outcomes data from an RCT, which looked at changes in functional status as measured by the Frenchay Activities Index (Schuurman et al 2000). This paper found a difference of 4.7 (95% CI: 1.2, 8.0) mean change in scores for DBS patients over thalamotomy patients (measured at 6 months). Using the cost data provided in the MSAC (2001) report, the extra cost of a 4.7-point change in the Frenchay scale would be $23,559 (which, as noted, is likely to be an underestimate).

Using the Australian cost data converted from UK pounds, a 4.7-point improvement on the Frenchay scale would incur an extra cost of between $17,830 and $51,385. To calculate this incremental cost, assumptions were made that the costs and the improvements in some aspects of simple daily tasks from DBS would continue for a five-year period, at the same level over ablative surgery. However the report concludes that the value patients would put on this gain in terms of preferences is not clear. Therefore it is not possible to establish whether or not DBS offers substantial improvements in QoL over the long-term.

Costing studies

A search of the literature found two modelled cost-effectiveness analyses (CEA) of DBS in the treatment of PD (Table 22).

Table 22 Modelled cost-effectiveness analyses of DBS in the treatment of PD

Author	Tomaszewski KJ, Holloway RG	Tomaszewski KJ, Holloway RG
Article Title	Deep brain stimulation in the treatment of Parkinson's disease: A cost-effectiveness analysis	Deep brain stimulation in the treatment of Parkinson's disease: A cost-utility analysis
Journal Name	Neurology	22nd annual meeting of the society for medical decision making
Journal Date	2001, 57:663–671	September 24–27, 2000 Hyatt Regency Cincinnati, Cincinnati, Ohio
Publication status	Published in a peer reviewed journal	No
Countries of authors	USA	USA
Type of article	Applied study	Applied study
Type of economic evaluation	Cost-utility	Cost-utility
Technology assessed	Bilateral DBS of the STN or GPI	DBS
Source of probability of main clinical events	Case series, estimates	Case series, estimates
Quantities of resources used	Pulse generator replacement every 3 years	Not specified
Prices or costs of resources	Professional opinion, Medicare reimbursement rates, hospital billing department (US$) for similar procedures	Medicare reimbursement rates used if possible (US$)
Outcomes	UPDRS and QoL	QoL
Outcome measure	QoL (estimated)	QoL (estimated)
Costs included	Additional DBS specific Initial surgery: • Follow-up calibration • 3- (2-to 5-) yearly pulse generator replacement • 10 additional physician visits over first 3 months • 4 additional visits from 3 to 6 months • Temporary DBS complication • Permanent DBS complication • No additional DBS-specific visits required past 1 year Both arms of model: • Annual drug costs ($4,447.90) • Annual physician visits, 4/year • Annual home care • Annual age-specific nursing home care	DBS procedural costs of $38,000 and 3-yearly battery replacement costs of $4,000
Costs discounted	3% (0–7%)	Not specified
Sensitivity tested	Yes (one-way sensitivity analysis)	Yes (one-way, variable and values not specified)
Study question	From a societal perspective, what are the life-time costs and benefits of DBS compared to best medical management in late stage PD	Not specified
Key results	Under base case assumptions, DBS when compared to best medical management has an ICER of US$49,000/QALY	Under base case assumptions, DBS has an ICER of US$20,900/QALY
Patient Group	PD patients aged 50 years or older who are in the later stages of the disease (Hoehn and Yahr stage between 3 and 5) with intractable motor fluctuations (Three ADL impairments)	PD patients aged 50 years or older who are in the later stages of the disease
Sponsor	NSRA/AHRQ pre-doctoral training grant. No commercial support	Not specified

Abbreviation: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Assumptions in the model:

- Patients enter the model at age 55 with three ADL level impairments and receive either DBS or SMT.

- Percentage changes in the UPDRS are assumed to correlate to similar percentage changes in QoL. All patients were assumed to enter the model with a base-case utility level of 0.55 (end-stage PD). The base-case DBS effect on QoL for successful surgery was assumed to be 30 per cent (utility=0.72) for four years (range 2–6 years), after which this improvement was assumed to decline linearly for a further five years at which point parity between patients in the DBS arm and SMT arms was assumed.

  The 30 per cent improvement was estimated from the published case series that reported a relative improvement in the OFF state of 25 to 50 per cent, and an average ON state improvement of approximately 15 per cent. Patients with permanent complications from DBS surgery (5.4%) were modelled to have a 20 per cent decrease in QoL (utility=0.44), while those with temporary complications from DBS surgery (28.2%) had a 12.7 per cent increase in QoL (utility=0.62) for 1.5 years, after which they were assumed to have equal QoL to patients with successful DBS intervention. The model assumes that 0.7 per cent of patients died as a result of DBS surgery.

- All patients enter the model at age 55 with three ADL impairments. Patients who receive DBS (with no or temporary complications) improve to one ADL. The model has calculated age-specific (with a neurological disease) and ADL-specific (zero, three and five impairments) probabilities for nursing home entry based on a study that used a multivariate proportional hazard model to identify the nursing home entry risk (Liu et al 1994). Therefore the probability of entering a nursing home is a function of age and DBS outcome. Permanent complications from DBS result in five ADL impairments. As with the QoL assumptions, the annual rate of nursing home entry for patients with successful DBS intervention (and those patients with temporary complications) was held constant (at one ADL level) over four years. The risk of entering a nursing home gradually increased during the following five years until, after nine years, the risk of entering a nursing home was the same age equivalent rate for patients in the SMT arm of the model. It was assumed that patients admitted to a nursing home would remain there. The model does not allow for short-term nursing home stays, including those for rehabilitation after falls. This assumption is likely to overestimate nursing home costs in the SMT arm because Liu et al (1994) reported that one-fifth of nursing home admissions are for stays of up to only 90 days.

- Patients receiving DBS that was successful or had only temporary complications required 43 per cent less pharmacotherapy. This reduction was applied at a constant and diminishing rate based on the same assumptions about time horizon of DBS-effectiveness as assumed for QoL and nursing home entry.

The key driver of this model was the assumption that the benefits of DBS over SMT result in at least a 30 per cent improvement in QoL and that this additional benefit lasts for nine years, though declining, for patients in the DBS arm over similar aged patients who receive SMT. For the first four years, these benefits are a fixed

additional increase in a patient's QoL and a fixed reduction in the probability of nursing home entry (and hence a reduction in nursing home costs). For the following five years these additional benefits decrease linearly until parity is reached with patients in the SMT arm.

The authors are transparent in stating the source of their evidence for the estimates used in the model. Usually, best guess is used. However, there are two issues with translating percentage improvements in UPDRS III into percentage improvements in QoL. Firstly, UPDRS III only measures the motor symptoms of PD, not changes in any of the other symptoms of PD, which will also impact on QoL. Secondly, there is a methodological issue that means percentage changes in UPDRS are not translatable into percentage improvements in QoL.

The model is sensitive to the assumed QoL benefit and the length of this benefit. Therefore assumptions that QoL only increased between 18 and 30 per cent resulted in incremental cost-effectiveness ratios (ICERs) of between US$50,000/QALY and US$100,000/QALY and a QoL increase of <18 per cent resulted in ICERs of >US$100,000/QALY. The study also reported that DBS may not be cost-effective when the length of the constant benefit of DBS over SMT (four years) was varied to less than three years and when the follow-up period during which the benefit decreases linearly was assumed to be less than the base-case of five years, and when DBS costs were >US$37,000. The model also assumes no further costs for DBS beyond 12 months, which is not realistic given the need for battery replacement.

Other costing studies

Two German studies have evaluated the health care utilisation of patients with PD who received STN DBS. The study by Spottke et al (2002) of 16 consecutive patients (recruited from two German centres) was prospectively evaluated over a period of 12 months. The cost-effectiveness of STN DBS was evaluated by calculating the incremental costs of patients treated with STN DBS against the drug costs at baseline using the UPDRS as an outcome measurement. Costs were from the perspective of the health care provider and were direct costs including drug treatment, in-patient hospital care (including the cost of surgery and the device) and out-patient hospital care. Adverse events were not costed.

Reductions in costs were the result of reductions in drugs used pre-and post-operatively. The ICER was reported as US$940 for a one-point decrease in the UPDRS score at 12 months. This study assumed that the pre-operative drug costs would remain the same for the next 12 months and not increase for patients treated with SMT as the disease progressed. The approach used in this study, in which pre- and post-operative health states were compared has the potential to underestimate the drug costs in the comparator arm and overstate the effect (or underestimate the effectiveness in the intervention arm if DBS is found to have a neuroprotective effect). The effect on the ICER cannot be estimated.

Meissner et al (2005) assessed the treatment costs of 46 patients for one year before and two years after STN DBS. This study included some of the patients from the study by Spottke et al (2002). Drug, in-patient admissions, surgical and outpatient care costs were included in total costs. UPDRS III scores before and after surgery was used as the measure of clinical efficacy. The study found that total treatment costs were increased by 32 per cent for the first year and decreased by 54 per cent for the second year when compared to pre-operative values and that the UPDRS III score was significantly

improved. Reductions in costs mainly resulted from a reduction in drugs after surgery. Although out-patient costs did not change, admission costs decreased for reasons that were not reported. Meissner et al (2005) concluded that STN DBS pays off from the second year while motor symptoms are improved. This study included the cost of patients with complications, but was not long enough to include battery replacement costs. Similar to the study of Spottke et al (2002), comparison of pre- and post-operative health states has the potential to underestimate the drug costs in the comparator arm and overestimate or underestimate the effectiveness in the intervention arm.

A number of studies have assessed the cost of caring for patients with PD. A 1997 study of 109 patients by Whetten-Goldstein et al (1997) estimated the annual societal burden of PD to be US$6,115/patient (in 1994 dollars), with the major direct costs being hospital and medical care. Lost earnings were included and found to be the largest cost component overall. A 1997 study by Rubinstein et al (1997) used the US National Medical Expenditure survey for 1987 of non-institutionalised civilians to estimate the costs associated with treating patients with PD to be $US10,168 compared to $US4,743 for the control group.

A study by Dodel et al (1998) that followed 40 outpatients with PD for 3 months found the average cost per patient to be $US3,390. Drugs were the major cost component, followed by hospital care. This study also found that on average, patients with dyskinesias cost approximately double that of patients without dyskinesia (US$4,260 compared to $US1,960).

A UK study (McIntosh et al 2003) estimated the actual costs of the procedure, but was published too soon after the introduction of the procedure to allow the estimation of other costs or benefits.

Comparator

The specific question to be answered by this application for continued funding is whether DBS is more effective than SMT. Standard medical therapy was assessed to be the next best treatment for PD patients who met the eligibility criteria for treatment with DBS because ablative surgery is rarely performed in Australia for this condition and therefore it was not possible to cost ablative surgery for PD in the current Australian setting.

Resource Costs

Hardware

The DBS system can be implanted as:

- two separate systems, each consisting of an IPG (Soletra), an extension and a deep brain electrode lead; or
- a system of one IPG (Kinetra), two extension leads connected to the IPG and two deep brain electrode leads.

Table 23 presents the current pricing for the components of a Medtronic Activa DBS system.

Table 23 Cost components of DBS

Item	Quantity	Price/unit ($)	Cost ($)
Kinetra			
IPG	1	14,622	14,622
Two extension leads	2	4,035	8,070
Two deep brain electrode leads	2	2,100	4,200
Patient activator[a]	1	1,352	1,352
Total cost of Kinetra system			28,244
Soletra			
IPG	2	8,923	17,846
One extension lead	2	4,035	8,070
One deep brain electrode lead	2	2,100	4,200
Patient activator[a]	1	1,352	1,352
Total cost of Soletra system			31,468

Source: MSAC application 1092

[a] The patient activator allows the patient to adjust the stimulation as necessary across a pre-set range of parameters

Procedure

As this procedure has already received interim funding MBS Items and their fees have been assigned to DBS (Table 24).

Table 24 MBS Items relevant to DBS

Item Number	Description	Fee ($)
40850	Deep Brain Stimulation for Parkinson's disease (unilateral), functional stereotactic procedure including computer assisted anatomical localisation, physiological localisation including twist drill, burr holes craniotomy or craniectomy and insertion of electrodes (Anaes) (Assist)	1,921.45
40851	Deep Brain Stimulation for Parkinson's disease (bilateral), functional stereotactic procedure including computer assisted anatomical localisation, physiological localisation including twist drill, burr hole craniotomy or craniectomy and insertion of electrodes (Anaes) (Assist)	3,362.60
40852	Deep Brain Stimulation for Parkinson's disease (unilateral), subcutaneous placement of neurostimulator receiver or pulse generator. (Anaes) (Assist)	289.00
40854	Deep Brain Stimulation for Parkinson's disease (unilateral), revision or removal of brain electrode (Anaes)	446.60
40856	Deep Brain Stimulation for Parkinson's disease (unilateral), removal or replacement of neurostimulator receiver or pulse generator (Anaes)	216.75
40858	Deep Brain Stimulation of Parkinson's disease (unilateral), placement, removal or replacement of extension lead (Anaes)	446.60
40860	Deep Brain Stimulation for Parkinson's disease (unilateral) target localisation incorporating anatomical and physiological techniques, including intra-operative clinical evaluation, for the insertion of a single neurostimulation wire (Anaes)	1,716.30
40862	Deep Brain Stimulation for Parkinson's disease, electronic analysis and programming of neurostimulator pulse generator (Anaes)	160.90

Source: Health Insurance Commission (HIC)

According to expert opinion, most surgeons in Australia prefer to implant the Soletra IPG as the unit is smaller. Table 25 presents the Medicare benefits for one patient with a bilateral implant and Table 26 provides the cost to replace the IPG.

Table 25 Medicare Costs for insertion of bilateral implant over 5 years

MBS Item	Description	Fee ($)	Quantity per patient	Total cost ($)
40851	Bilateral implantation of electrodes	3,362.00	1	3,362.00
40852	Unilateral implantation of IPG	289.00	2	578.00
40860	Unilateral target localisation (neurologist)	1,716.30	2	3,432.60
40862	Programming	160.90	12	1,930.80[a]
(Discounted at 5%)				(1,741.53)
			Total	9,303.40
			(Discounted)	(9,114.13)

Source: MSAC application 1092 and HIC data
[a] Based on 2.5 adjustments/year (if assumed that four visits/year cost=$3,218)

Table 26 Costs of replacement of the IPG over 5 years

Item	Fee/Price per unit ($)	Quantity	Total cost ($)
Unilateral removal or replacement of IPG (MBS Item 40856)	216.75	2	433.50
Soletra	8,923.00	2	17,846.00
		Total (one every 5 years)	18,280.00
		(Discounted at 5%)	(15,791.00)
		Total (one every 3 years)	25,591.00
		(Discounted at 5%)	(21,520.00)[a]

Source: MSAC application 1092 and HIC
[a] One replacement discounted at year 3, and 0.4 of a replacement discounted at year 5

In providing the anticipated costs for the DBS system over a period of five years, the Applicant has assumed that the IPG battery will require replacement once every five years and a patient will require 12 visits in total to adjust their IPG. Rodriguez-Oroz et al (2004) reported a mean post-operative period of 46 months (range 36–52) before batteries required replacement. The previous MSAC evaluation for DBS funding (MSAC 2001) assumed that IPG battery changes would be required every three to five years. Therefore the total undiscounted cost of $18,280 (Table 26) is probably an underestimate and the actual figure might be as high as $25,591.

The estimates in Table 25 assumed an average of 2.5 follow-up visits per year for adjustment of the stimulator. As acknowledged in the previous MSAC evaluation, it is difficult to quantify how many visits are required for adjustment of the IPG as patients will respond differently. In estimating the potential cost of DBS based on cost data from the UK, the previous MSAC application provided a conservative estimate of one stimulator adjustment per year in the base case analysis, varied to four times per year to estimate a maximum cost (Table 19, MSAC 2001).

Patients undergoing a DBS procedure will incur in-patient hospital costs in addition to surgical costs.

Intracranial stereotactic localisation (code 4080300) falls within three Australian Refined Diagnostic Related Groups (AR-DRGs):

- B02A: Craniotomy with catastrophic complications or co-morbidities

- B02B: Craniotomy with severe or moderate complications or co-morbidities
- B02C: Craniotomy without complications or co-morbidities

Table 27 lists the average inpatient costs that may be incurred.

Table 27 Private hospital casemix data for DBS-relevant DRGs

DRG	Number of separations[a]	ALOS (Days)	Average cost per AR-DRG ($)
B02A	352	20.11	16,442
B02B	498	11.76	9,768
B02C	1,108	8.42	7,897

[a] Data are for August 2002

It is assumed that patients with PD are unlikely to be admitted under B02C as it excludes patients with co-morbidities such as PD. DRG BO2A includes patients who are very unwell, and may not therefore be candidates for a DBS system, so it is assumed that a patient admitted for insertion of a DBS system will fall under the BO2B DRG and incur average in-patient hospital costs of $9,768 in addition to the costs of the actual procedure. Use of DRG BO2B assumes in-patient days of 11.76 including both pre-operative and post-operative days. McIntosh et al (2003) assumed a longer period of 13 post-operative days and two pre-operative days, but expert opinion is that the duration of in-patient stays has decreased as surgeons have gained experience.

The nature of surgery for DBS requires that patients have pre-surgery planning, which is likely to vary across the specialised centres. Table 28 lists the likely additional costs but excludes costs that may be routine at some centres but not others, such as the cost of a psychologist to administer psychological testing.

Table 28 Costs associated with surgical implantation

Item	Description	Fee ($)	Quantity	Cost ($)
63010	MRI scan of the brain for the purpose of planning for stereotactic neurosurgery	336.00	2	672.00
21922	Initiation of management of anaesthesia for computerised axial tomography scanning, magnetic resonance scanning, digital subtraction angiography scanning	117.95	2	235.90
17603	Examination of a patient in preparation for administration of an anaesthetic relating to a clinically relevant service	36.40	2[a]	72.80
20210	Initiation of management of anaesthesia for intracranial procedures	252.75	1	252.75
20400	Initiation of management of anaesthesia for procedures on the skin or subcutaneous tissue of the anterior part of the chest	50.55	2[a]	101.10
			Total	1,334.55

[a] This includes insertion and replacement procedures

According to expert opinion, patients on average require two MRI scans to assist in planning the stereotactic surgery.

Complications

Other important costs are those associated with any complications arising from implantation of a DBS system during or after surgery. The safety evaluation found complications during surgery to include misplacement, dislocation and fracture of electrodes, erosion of the skin, formation of seroma in the subcutaneous pocket receiving the IPG, haemorrhage and infection. Table 12 of this Assessment Report, provides details of the procedure-related adverse events. Only one of the case series reported an irreversible outcome (ischaemic stroke resulting in persistent neurological deficits).

After-surgery complications include hardware-, environment- and stimulation-and target-related side effects and complications. The safety evaluation found that hardware-related complications, such as electrode fracture and dislocation, and hardware failure, can occur at any time after surgery but are reversible through removal of the system or parts of it and re-implantation of new components (Table 13). It was not clear whether the mortality reported in two case series was due to the procedure or subsequent use of the stimulator. Reports of hardware-related complications ranged from 1.4 to 46.0 per cent, of which stimulation- and target-related complications were the most frequent problems. While these may be reversible, correction of the problems may lead to reduced efficacy of DBS.

Some of these complications were irreversible though others, such as weight gain, might not indicate the need for cessation of treatment. Joint et al (2002) reported a rate of hardware-related problems of 20 per cent from April 1998 to March 2001, noting that the number of problems declined with increased experience of the clinicians and that some problems may be idiosyncratic of the methodology of individual groups.

Safety data provided to the US Food and Drug Administration (FDA) for pre-market approval indicated that 96.3 per cent of enrolled patients experienced one or more

permanent or temporary adverse events, including intracranial haemorrhage, haemiplegia/haemiparesis and device related-infections over the 12 months. There were no deaths recorded directly resulting from surgery. Of the 289 systems implanted, eight were removed and three were replaced during the clinical study (a total of 2.7% of systems). Thirty leads of the 293 implanted were removed, of which 20 were replaced (10.2% of leads). It is not clear whether these events occurred in separate patients or one patient had more than one procedure resulting from hardware failure. The Applicant states that the rate of device-related events was 36.9 per cent and that the rate of ongoing device-related events (this was a 12-month study) was 10 per cent (current MSAC Application).

From the evidence the rate of complications, especially those related to the hardware, appears to have been relatively high early in the life of this procedure but has decreased with experience. Each complication will affect the cost-effectiveness of DBS due to the increasing cost associated with replacement of leads or generators as well as any reduction in benefit resulting from a temporary or permanent decrease in the efficacy of DBS to below the levels reported in the case-control studies. Any permanent complications may also incur additional costs.

A 2003 UK study (McIntosh et al 2003) estimated the discounted costs (at 6%) of hardware failure over five years to be £4,246 ($A9,956, using an exchange rate of £1=$AUD2.354 http://www.xe.com/ucc/). To estimate this amount, probabilities of lead fracture (5% of patients), infection (1.5% of patients) and skin erosion (2.5% of patients) were sourced from Oh et al (2001).

Table 29 summarises the estimates in Tables 23-28 of the cost of the DBS procedure.

Table 29 Summary of costs of DBS

Cost Items	Intervention	Comparator	Incremental difference	
	DBS-STN ($)	SMT ($)	Costs incurred in 1st 12 months ($)	Costs discounted at 5% ($)
Cost of Soletra system	31,468	0	31,468	
Cost of insertion of bilateral implant	9,303	0		9,114
Cost of replacement IPG	18,280–25,591	0		15,791–21,520
Other cost s associated with surgery			1,335	
Cost of in-patient stay	9,768	0	9,768	
Cost of complications[a]	9,956[b]	0		9,956[b]
Total incremental discounted costs				77,432–83,161

Note: all estimates have been rounded
[a] McIntosh et al (2003)
[b] Discounted at 6%

The cost of the procedure is estimated to be $67,475–$73,204 discounted plus any costs associated with surgical- or device-related complications over five years. If the estimates from the study by McIntosh et al (2003) of the cost of complications are included, then total costs are estimated to be $77,432–$83,161 over five years. The majority of the costs for implantation of a DBS system are incurred at the time of the procedure or in the first 12 months after surgery.

The incremental cost of DBS compared to SMT is greater than that of the previous MSAC assessment in which DBS was compared to ablative surgery. The reason is that both DBS and ablative surgery have common surgical costs that are absent from SMT. The study by McIntosh et al (2003) estimated the total discounted cost of insertion of a STN DBS over a five-year period at £32,526 ($A76,270; using an exchange rate of £1=$AUD2.354 http://www.xe.com/ucc/), assuming battery replacement once every five years. Costs were estimated based on a bilateral procedure using the Kinetra system (which is cheaper than the Soletra system, see Table 23) and include the costs of complications. The study found that initial cost of the equipment and likely follow-up replacement of the equipment accounted for 70 per cent of costs. The study did not include direct costs incurred by patients, informal care or productivity losses, but acknowledged the importance of these factors.

Given that PD is a chronic illness, a more complete assessment of the total cost of DBS intervention in the overall picture of end-stage PD should include the remaining lifetime costs of patients treated with DBS and those treated with SMT. Five years is not a sufficiently long enough time horizon in which to judge the long-term effects of DBS on the ongoing treatment and care of patients with PD. This is because the electrodes remain in place for as long as they are assessed to be working, which may be much longer than the five years of this economic evaluation. Also, STN DBS may delay or avoid future costs that have been incurred in the SMT arm. The estimated costs presented above are gross costs; they do not include any cost offsets in the form of reduced future costs to the health system resulting from an improvement in patient morbidity.

Cost savings

The insertion of a DBS system incurs upfront costs but may result in cost savings from its effect of controlling the motor symptoms of PD as disease progresses, allowing patients to live in more functional health states for longer periods of time with improved QoL. To date, there appears to be no evidence that DBS delays the progression of PD or affects the mortality rate, although it may be argued that mortality due to falling, for example, may decrease with improvements in motor skills. These savings could be realised through a reduced demand for services or a lower expenditure on certain services as follows:

- Patients with a DBS system have less need for a given level of pharmacotherapy than similar patients receiving SMT.
- Improved levels of ADL reduce the need for community services, such as visits to GPs and visits by nurses.
- Improved levels of ADL impairment results in reduced need for entry into nursing homes.
- Patients with a DBS system have improved motor skills and therefore a reduction in the requirement for allied services, such as physiotherapy.
- Improved motor skills may result in a reduction in the incidence of falls or pneumonia and the treatment costs that they require, such as hospitalisation.

Data concerning the incremental benefit of DBS compared to SMT in clinical trials is needed to quantify these cost savings.

Outcomes

Pharmacotherapy

There is strong evidence to show that DBS decreases the need for pharmacotherapy. Three of the included studies reported the total LEDDs as outcome measures. Rodriguez-Oroz et al (2004) reported a 50 per cent reduction four years after surgery in the LEDD, which decreased from 1,287.5 mg (range 300–2,050 mg) pre-operatively to 641 mg (range 140–1,140 mg) post-operatively. Capecci et al (2005) reported a decrease of 33 per cent in the LEDD of the DBS group compared to an increase in the SMT arm over a 12 month period. The 24-month data shows continuing reductions in LEDD of 50 per cent compared to baseline for patients who received DBS, however the data were incomplete as not all patients in this group had completed 24 months of the study.

Hjort et al (2004) reported a reduction of 29 per cent in LEDD from 1,138 mg to 813 mg. The systematic review of the case series of bilateral STN DBS by Hamani et al (2005) also reported that LEDDs were reduced by 47 per cent at 12 months and 59 per cent at 60 months. This evidence is supported by Australian case series studies (Table E5, Appendix E) reporting pre- and post-operative LEDD in patients with STN DBS. Four of the five studies reported reductions in LEDD of between 29.6 to 81.8 per cent. Only one study reported no significant difference.

Although LEDD is the common trial endpoint used in the studies to calculate reduction in L-dopa equivalent dose, the drugs for calculating LEDD differed between the studies. For example, the Rodriguez-Oroz et al (2004) study cites The Deep Brain Stimulation for Parkinson's Disease Study Group (2001) that calculated the levodopa daily consumption using the following standard equivalents:

- 100 mg of standard levodopa equals 133 mg of controlled-release levodopa equals 10 mg of bromocriptine equals 1 mg of pergolide.

However, Capecci et al (2004) used the following formula to calculate LEDD (citing Moro et al 1999):

- Levodopa controlled-release preparations, 0.77; bromocriptine, 10; apomorphine, 50 and pergolide, 100.

Esselink et al (2004) included more drugs in the conversion formulation as follows:

- Regular levodopa dose x1 + Slow-release levodopa x 0.75 + Bromocriptine x 10+Apomorphine x 10 + Ropinirole x 20 + pergolide x 100 + Pramipexole x 100 + [regular levodopa dose + (slow-release levodopa x 0.75)] x 0.2 if taking entacapone.

LEDD is calculated according to a patient's individual medications and then averaged across the study or study arm. It does not appear that there is a standard drug combination for patients in late stage PD or even a 'typical' patient as patients appear to have a degree of autonomy in adjusting their dosages according to symptoms. This makes it difficult to derive an average LEDD as a basis for costing. To estimate drug costs, case series data provided by the Applicant have been used to determine the typical

drugs, dosage, daily and yearly costs and pre-and-post operative reductions in each of these drugs for a 'typical' patient. Table 30 presents this information.

Table 30 Pharmacological base case for a 'typical patient' derived from case series data

Drug	Average daily dosage (mg)	Average daily cost/per patient[b] ($)	Average yearly cost /per patient ($)	Proportion of patients using drug pre-operatively (%)	Proportion of patients using drug post-operatively (%)	Reduction post-operatively[c] (%)
Levodopa+Carbidopa (DDD=600 mg)	1,075	4.183[d]	1,526.73	100.0	87.5	55.5
Controlled-release levodopa (Sinemet CR)[a] (DDD=600 mg)	367	0.897[e]	327.47	75.0	12.5	45.5
Pergolide (DDD=3 mg)	3.5	2.164[f]	789.72	25.0	0.0	100.0
Apomorphine	145	23.106[g]	8,433.60	25.0	0.0	100.0
Cabergoline (DDD=4 mg)	3.7	1.281[h]	467.50	38.0	25.0	11.0
Entacapone (DDD=1 gm)	1,200	6.497[i]	2,371.36	75.0	0.0	100.0
Selegiline (DDD=5 mg)	5	0.071[j]	25.81	12.5	12.5	–50.0
Amantadine (DDD=200 mg)	200	0.214[k]	77.93	25.0	0.0	100.0
Average weighted cost per patient						
		Daily	Yearly			
Pre- operatively		38.41	14,020.11			
Post-operatively		2.61	952.35			
Five-year cost savings discounted at 5% :			57,199			

Source: Case series data provided by Applicant

Abbreviations: DDD, defined daily dose per thousand of the population per day. This is the assumed average dose per day of the drug used for its main indication by adults (including both early- and late-stage PD patients). The DDD is included to allow comparison with the average doses of patients in the study. A DDD for Apomorphine is not yet available. Source: Australian Statistics on Medicine (2003).

[a] Note: This is an average daily dose of the patients in the case series and is not meant to reflect an actual dose. An actual dose of 2 tablets would equal 400 mg levodopa/100 mg carbidopa

[b] Drug prices from Schedule of Pharmaceutical Benefits, 1 August 2005 (all drugs are dispensed price only, premium pricing is not included)

[c] This is the percentage reduction in the average daily dose of the drug as reported in the case series (so included in the percentage are patients no longer using that drug, using less of the drug or in the case of selegiline using more of the drug)

[d] Kinson 100 mg–25 mg (100 tablets)

[e] Sinemet CR 200 mg–50 mg (100 tablets)

[f] Permax 1 mg (100 tablets)

[g] Apomine 10 mg/1 mL injection (Pack size 5)

[h] Cabaser 4 mg (30 tablets)

[i] Comtan 200 mg (200 tablets)

[j] Selgene 5 mg (100 tablets)

[k] Symmetrel 100 mg (100 capsules)

To calculate the average weighted cost per patient an average daily dose of each drug was estimated using the patients in the case series. This average daily dose was then multiplied by the cost per mg of each drug and weighted by the proportion of patients who received it pre-operatively. This typical patient reflects the probability that a patient with PD will be on any of these drugs. The weighted average cost per patient per year was estimated at $14,020 pre-operatively and $952 post-operatively, a saving of $57,199/patient discounted over a five-year period. The five-year time frame is a

reasonable assumption given the results from the Rodriguez-Oroz et al (2004) study showing that patients maintained a 50 per cent reduction in LEDD from baseline four years after the procedure.

It appears that the drugs no longer required are the more expensive late-stage drugs typically used to control symptoms associated with long-term and increasing doses of levodopa. For some patients, it appears that pharmacotherapy is no longer required to control PD symptoms. The discontinuation of apomorphine is supported in the literature. Limousin et al (1998) reported that nine out of 10 patients discontinued apomorphine 12 months after receiving DBS.

However, while the amounts estimated in Table 30 give some indication of likely substantial drug savings they need to be considered with some caution. Firstly, the included studies in the evaluation section of the report did not include the individual drugs and dosages of the patients included. Therefore the drugs included in Table 30 may not accurately represent the pharmacotherapy of patients included in these trials and from which efficacy data were obtained. Secondly, the estimates are derived from only one case series in which the number of patients was small and the proportion of patients who used drugs other than levodopa may change, if a different case series were presented, there is therefore likely to be considerable variability in the figures.

Expert opinion suggests that the dosage and post-operative reduction of entacapone is particularly subject to variability. Specifically, the dosage of entacapone in Table 30 is at the higher end of the expected range and that post-operatively the dosage of entacopone may reduce in proportion to the reduction in levodopa. Table 31 presents a sensitivity analysis of the data provided in Table 30 based on this expert opinion.

Table 31 Sensitivity analysis

Drug	Average daily dosage (mg)	Average daily cost/per patient[b] ($)	Average yearly cost /per patient ($)	Proportion of patients using drug pre-operatively (%)	Proportion of patients using drug post-operatively (%)
Levodopa+Carbidopa	1,075	4.183[c]	1,526.73	100.0	87.5
Controlled release levodopa (Sinemet CR)[a]	367	0.897[d]	327.47	75.0	12.5
Pergolide	3.5	2.164[e]	789.72	25.0	0.0
Apomorphine	145	23.1063[f]	8433.60	25.0	0.0
Cabergoline	3.7	1.281[g]	467.50	38.0	25.0
Entacapone	1,000	5.414[h]	1976.13	75.0	25.0
Selegiline	5	0.071[i]	25.81	12.5	12.5
Amantadine	200	0.214[j]	77.93	25.0	0.0
Average weighted cost per patient					
		Daily	Yearly		
	Pre-operatively:	37.33	13,624.88		
	Post-operatively:	4.41	1611.06		
Five-year cost savings discounted at 5% :			52,586		

[a] Note: this is an average daily dose of those patients in the case series and is not meant to reflect an actual dose. An actual dose of 2 tablets would equal 400 mg levodopa/100 mg carbidopa
[b] Drug prices from Schedule of Pharmaceutical Benefits, 1 August 2005 (all drugs are dispensed price only, premium pricing is not included)
[c] Kinson 100mg–25 mg (100 tablets)
[d] Sinemet CR 200 mg–50 mg (100 tablets)
[e] Permax 1 mg (100 tablets)
[f] Apomine 10 mg/1 mL injection (Pack size 5)
[g] Cabaser 4 mg (30 tablets)
[h] Comtan 200 mg (200 tablets)
[i] Selgene 5 mg (100 tablets)
[j] Symmetrel 100 mg (100 capsules)

Changes to the pre-and post-operative dosage of entacapone listed in Table 31 had a slight effect on the estimated cost savings for pharmacotherapy. The overall estimated reductions in the use of the drugs from the case series (Table 30) were consistent with the figures quoted in the case-control studies for patients who had received DBS and which reported no reduction in the pharmacotherapy of the control patients (Capecci et al 2005) The cost savings were estimated by assuming that the average weighted drug regimen of patients pre-operatively, which gives an estimate of SMT, will remain the same. To the extent that patients deteriorate over five years and require increasing doses and new drugs added to their regimen to control symptoms, these estimated savings may underestimate the total savings on drug costs.

There may also be savings accruing to individual patients. Under the Pharmaceutical Benefits Scheme (PBS) patients are required to pay a co-payment for each script filled. The co-payment can range from $4.70 to $29.50, depending on whether the patient is classified as general or concessional. For patients with late stage PD who are chronically ill and likely to be on a pension, the co-payment is likely to be $4.60. Currently, individuals can incur out-of-pocket expenses up to the safety net threshold of $960.10 for general patients and $253.80 for concessional patients before the co-payment is waived. Therefore, a reduction in the number of scripts required to be filled may reduce the out-of pocket expense for individual patients.

Trial endpoints measuring motor symptoms

The included studies all appear to show a statistically significant sustained benefit in motor symptoms and disability compared to pre-operative baseline symptoms for patients who have received DBS compared to those receiving SMT. They found a significant improvement in the UPDRS III motor score in the medication OFF (stimulation-on) state and no change in the ON medication (stimulation-on) state compared to controls, which is likely to be related to disease progression. UPDRS-ADL scores also showed a benefit in favour of DBS. The double-blind crossover study (Rodriguez-Oroz et al 2004) and two case-control studies (Capecci et al 2005, Just & Ostergaard 2002) found that motor features that were especially resistant to levodopa, such as speech, appeared to deteriorate.

The highest level of effectiveness data available is that from the double-blind crossover study by Rodriguez-Oroz et al (2004), which reported that at four years in the OFF medication state a 17 point reduction in the mean UPDRS III score (that is a decrease from 43 with stimulation off to 26 with stimulation on).

The primary clinical outcome measure of the Capecci et al (2005) study was a reduction in the UPDRS-ADL score. Patients in the DBS arm had a score of 16.6 at baseline, 8.0 at 12 months and 10.6 at 24 months (which included data from only 57% of the study participants). Patients in the control arm went from a score of 14.4 at baseline to 14.9 at 12 months and 16.3 at 24 months (which included data from only 50% of patients due in part to some of these patients enrolling for the DBS procedure). The UPDRS III OFF score at baseline for patients who received DBS was 38.3 decreasing to 17.9 at 12 months and 24 months. In comparison, patients in the control arm had a baseline score of 37.4 that increased slightly over the two-year period of assessment.

Although the results from the Rodriguez-Oroz et al (2004) study indicated that the benefits of DBS lasted for fours years, the Capecci et al (2005) study used a control arm which provides a better indication of any deterioration in motor symptoms experienced by patients in the SMT arm compared to those in the DBS arm. If DBS has a postulated neuroprotective effect, then a study with a control arm is better able to provide evidence of this additional benefit. Using the results from Capecci et al (2005) and assuming that any benefits last for five years, the incremental benefit of STN DBS as measured by the UPDRS-III OFF motor score at 24 months is 23.7 points and as measured by the UPDRS-ADL, is 5.7 points.

The study by Capecci et al (2005) has an outcome measure the OFF daily rate. This is a measure of the proportion of the day spent in the off-medication state, when the patient's symptoms, such as being unable to walk or feed themselves, are more evident. Capecci et al (2005) reported that the daily OFF rate decreased by 90% in all 23 STN DBS patients. Although the authors did not specify how they measured this outcome, it is usual to ask the patient to estimate the proportion of their waking day spent OFF on average. Using this as a guide, patients in the surgical arm appear to have gone from being in an OFF state for about 46 per cent of their waking time to less than 6 per cent, whereas the OFF state of control patients increased from 38 per cent to 46 per cent of waking time.

This is an important result as the other clinical endpoints used in the trials are difficult to translate into an average impact on a patient's condition. The improvement in the daily OFF rate for patients who had received STN DBS, despite progression of the underlying

disease at a similar rate for both groups of patients (as demonstrated by the lack of significant difference between the patients in the ON medication state) provides evidence of the ability of DBS to mimic the effect of the anti-parkinsonian medication, when it is working, resulting in substantially reduced waking periods when patients are affected by their parkinsonian motor symptoms.

Other resources

The five-year time horizon over which this procedure has been costed is insufficient to allow quantification of longer-term gains if the improvement in patients' ADL and control of their motor symptoms lasts beyond five years. These longer-term gains are likely to result from a reduction in falls and decreased impairment in ADL as a result of improved controlled of motor symptoms.

Falls are a problem for patients with PD. A US survey by Wielinski et al (2005) found that 55.9 per cent of PD patients had at least one fall in the previous two years. Sixty-five per cent of those sustained an injury, 33 per cent sustained a fracture (12% of the population), 75 per cent of injuries required health care services and 40 per cent of fractures required surgery. Age, disease duration, diagnosis of atypical parkinsonism and dementia were identified as significant risk factors for falls. Longer disease duration was an expected risk factor for falling as it is reported to be a proxy for the degree of progression of PD.

Limitations of the study were recall bias – recollection of falls may not always be reliable – and falls that incurred injuries may be over represented. Older age is a risk factor for falling in the general population and population-based samples of community-dwelling older people have shown the incidence of falling to be 28 to 35 per cent (Blake et al 1988, Campbell et al 1981, Prudham & Evan 1981, Tinetti et al 1988). A six-month study by Bloem et al (2001) found a 50.8 per cent risk of falling among 59 PD patients compared to 14.5 per cent among controls. Patients with PD are clearly at a greater risk of falling than patients from the general population and at a greater risk of fracture, 12 per cent compared to two to six per cent fracture risk after a fall for community-dwelling older people (Lord et al 2001). The greater risk of fracture associated with a fall is thought to result from lower bone density, lower bone mass and a high prevalence of vitamin D deficiency, which has been reported among patients with PD (Wielinski et al 2005).

A UK-based study (Woodford & Walker 2005) that identified patients with PD and then identified all emergency admissions of this subgroup, found that the primary reasons for emergency admission to hospital were falls (17%), pneumonia (13%) and decreased mobility/dyskinesia (8%). Compared to non-PD individuals over the same four-year period and admitted to the same ward, PD patients were likely to have an increased mean duration of hospital stay of 3.5 days, to be slightly younger (78 versus 82) and a greater likelihood of being male (52% versus 40.8%). Sixty-six per cent of PD patients returned home after hospital admission and 21 per cent required nursing home care. For non-PD patients, the corresponding proportions were 73 per cent and 15 per cent.

Guttman et al (2003) assessed the prevalence of PD and physician- and drug-related costs and hospital use compared with age- and sex-matched controls 1:2 (15,304 to 30,608) in Ontario. They found that, on average, PD patients were 1.45 (95% CI: 1.42, 1.48) times more likely to have an acute hospitalisation and their length of time in hospital was found to be 1.19 times more than controls. A limitation of this study is that patients were diagnosed from an administrative database by the use of the ICD-9 PD

diagnostic code (332) or specific PD drugs in the database, or both. There was no clinical validation of the diagnosis.

Although these studies all demonstrate that PD patients are at much higher risk of acute admission to hospital than the general population, most likely due to a fall, there are no studies that compare the rate of falls or hospitalisation between patients treated with DBS or SMT.

Attempts have been made to link trial outcomes to a reduction in health care resources. For example, Tomaszewski & Holloway (2001) used a reduction in admission to nursing homes for patients who had received DBS compared to patients treated with SMT, based on a reduction in the level of ADL impairment. The study assumed that patients who had received DBS would have an ADL impairment of 1 compared to SMT patients whose ADL impairment remained at the pre-surgery level of 3.

Estimates for the probability of entering a nursing home were based on a study by Liu et al (1994) that identified the risk of nursing home entry in 1982. Liu et al (1994) provided probabilities based on age, ADL impairments (zero, three and five) and neurological disease such as PD. These probabilities allowed Tomaszewski & Holloway (2001) to estimate annual disease disability-specific nursing home rates using the assumptions that all patients commence with three ADL impairments, and that patients who have DBS improve to one ADL impairment post-operatively, except for those who experience permanent complications.

The hazard rate of nursing home entry estimated by Liu et al (1994) does not differentiate between PD patients with and without dementia. Although Liu et al (1994) found in a two-year period that increasing levels of ADL impairment resulted in increasing probability of any nursing home admission, the relationship is reversed over the expected remaining lifetime because patients with high ADL levels have a higher risk of dying, which reduces their risk of nursing home admission. Liu et al (1994) reported that the probability of nursing home admission over remaining lifetime for someone with a history of neurological disease was 0.610 and with cognitive impairment 0.539.

Based on the current studies, it is not possible to quantify any differences in the rate of falls or admission to hospital for patients who have received DBS compared to patients treated with SMT. The evidence suggests that there is likely to be a difference in admission to hospital for falls or decreased mobility/dyskinesia, based on the improvement in motor symptoms, gait, freezing, postural reflex and falls reported in Capecci et al (2005). Savings may take the form of carer costs, demand for community-based care, acute hospital admissions and cost of nursing home admissions.

Indirect costs associated with DBS may be considerable. Although returning to full-time employment or household chores was not a clinical endpoint in the trials, Spottke et al (2002) reported that one of their 16 patients was able to return to full-time employment and the study by Moro et al (1999) reported that five housewives regained the ability to look after their families. Table 32 provides a summary of the reported costs and benefits of the procedure.

Table 32 Summary of discounted potential costs and benefits over 5 years

Variable	STN DBS	SMT	
			Incremental cost discounted at 5%
Cost of procedure ($)	70,1534–77,465	0	67,475–73,204
Cost of complications[a] ($)	9,956[b]	0	9,956[b]
Cost of pharmacotherapy ($)	60,700	4,123	(–57,199)
Cost of falls or nursing home costs			(–likely savings)
			20,232–25,961
			Incremental benefit undiscounted
UPDRS-III motor score: OFF medication state, difference between off and on stimulation Rodriguez-Oroz et al (2004)			17 points
UPDRS-III : OFF medication, ON stimulation (Mean±SD) Capecci et al (2005)[c,d]	18.0±4.7	41.7±7.9	23.70 (95% CI: 29.70, 17.66)
UPDRS-ADL: ON medication, ON stimulation (Mean±SD) Capecci et al (2005)[c]	10.6±3.3	16.3±7.9	5.70 (95% CI: 11.46, –0.06)
Daily OFF rate (Mean±SD) Capecci et al (2005)[c,d]	5.2±6.3	45.8±8.9	40.60 (95% CI: 47.65,33.55)

[a] McIntosh et al (2003)
[b] Discounted at 6%
[c] Scores at 24 months
[d] Secondary endpoint
Calculated using RevMan 4.2

The estimated extra cost of a 23.7-point change in the UPDRS-III over five years is $20,232–$25,961 discounted, depending on whether the assumption is that the IPG is replaced every three years or every five years (Table 32). The difference reported in Capecci et al (2005) was used to estimate this cost because the study included a control arm, which improves the likelihood of detecting any deterioration or improvement in either arm. A study with a control group is a better design to pick up any neuroprotective effects of DBS. A crossover designed trial as used by Rodriguez-Oroz et al (2004) would not be able to detect such a benefit. However, results from the Rodriguez-Oroz et al (2004) study demonstrated that the benefits from DBS remain after four years. Using the results at 24 months to estimate the difference between the two arms produced conservative results because no adjustment was made for the difference in baseline between the two groups (significance has not been reported) and only partial results for the cohorts were provided.

Quality of life

Just & Ostergaard (2002) define Health Related Quality of Life (HRQoL) as optimum levels of mental state, physical state, role (eg work, parent, carer, etc) and social functioning, including relationships and perceptions of health, fitness, life satisfaction and well-being. Quality of life measures seek to incorporate a patient's own perspective of their health. The PDQ-39SI is a Parkinson disease specific quality of life instrument and is intended to assess more areas of a patient's subjective well-being than are assessed by clinical scales. The PDQ-39SI has been shown to have good reliability, validity,

responsiveness and reproducibility (Just & Ostergaard 2002, Schrag et al 2000) and was administered at baseline (pre-surgery) and six months after surgery. The reduction in the PDQ-39SI score in the surgery group after six months was statistically significant while the score in the control group did not change. It is possible to say based on the results in Just & Ostergaard (2002) that at 6 months, using the PDQ-39 as a measure, health-related QoL for the surgical patients had improved. This is because patients who had had surgery had an improvement in all eight subscales of the PDQ-39SI. However, the PDQ-39SI score cannot be used in a cost utility analysis because the instrument has not measured QoL on the 0 (death) to 1 (full health) scale necessary to construct QALYs (Blumenschein & Johannesson 1996).

Various studies have attempted to determine what aspects of PD most affect patients. A population-based study by Schrag et al (2000) asked all patients identified with PD to complete a disease-specific QoL questionnaire (PDQ-39) and the Beck Depression Inventory (BDI) to identify the factors that determine QoL. Other instruments and assessments conducted were the Hoehn & Yahr scale, the Schwab and England disability scale, the UPDRS III, the mini mental state examination (MMSE) and two other QoL instruments (EQ-5D and short form-36). The authors concluded that in idiopathic PD, QoL is primarily determined by depression, disability, disease severity (particularly related to axial features) and cognitive impairment. The motor part of UPDRS did not correlate strongly with QoL scores. It was noted that the causality between QoL, depression and disability is difficult to establish.

A number of studies have looked at the effect of DBS on QoL. A review of the literature between 1965 and 2005 by Diamond & Jankovic (2005) identified eight studies that had HRQoL as an outcome in STN DBS. All eight studies, varying in length from three months to two years, reported HRQoL improvements of between 14 and 62 per cent, mainly using the PDQL instrument. Only one of these studies, in which 34 patients were randomised to unilateral pallidotomy or bilateral STN DBS provided level 1b evidence (Esselink et al 2004). There was a trend to significance for STN DBS over unilateral pallidotomy at six months, however the study failed to show statistical significance (reported as being due to a lack of statistical power). The longest study was two years (Lezcano et al 2004). It provided level II evidence. Fourteen consecutive patients were assessed using the PDQ-39, with ON medication at baseline (before surgery) and ON medication and ON stimulation during the follow-up. The improvement in QoL of patients two years after surgery was reported as 62 per cent.

A Finnish study by Erola et al (2005) of 29 successive patients, reported the individual PDQ-39 scores both before and 12 months after surgery. The authors found a correlation between patient's age and PDQ-39; younger patients showed a greater improvement. Of the subscales, only communication became worse during follow-up. This small study found a correlation between UPDRS-III scores and the PDQ-39.

Although, the benefits of STN DBS on the motor aspects of QoL are strongly supported, the effects on the non-motor symptoms appear more mixed. Using the clinician-based measure, the BDI, Capecci et al (2005) found no difference between patients who had undergone surgery and those in the control group. If anything, the trend in their data slightly favoured the control arm at 24 months. The study of Drapier et al (2005) assessed 27 consecutive patients who underwent STN DBS from 1999 to 2002 and concluded that patients showed significant improvement using the clinician based rating scale (UPDRS). However, using patient's self-assessment scales (PDQ-39, SF36), the clinical benefit of STN DBS was more subtle, with physical items of QoL

improved significantly but mental items such as emotional well-being, social support, cognition and communication did not improve. They concluded that their results were suggestive of a dissociation of motor and non-motor symptom control after bilateral STN DBS in PD patients. Patients were excluded from the study of Drapier et al (2005) if they showed cognitive impairment, marked cerebral atrophy or major depression.

A study by Gray et al (2002) attempted to measure the change in utility of patients following surgical treatment of PD, including one patient who had undergone DBS. The authors measured the baseline mean utility of 97 patients with PD who underwent unilateral thalamotomy, unilateral pallidotomy, bilateral pallidotomy, STN lesions, mixed lesions or bilateral STN DBS at 0.56 by a rating scale method or 0.66 by the time trade-off method of valuation. The patients who had a bilateral pallidotomy had the best response post-operatively, reporting a 23 per cent improvement in the QoL (utility =0.64) using the rating scale method and an 11 per cent improvement in QoL (utility=0.69) using the time trade-off method.

Usage

PD is one of the most common neurodegenerative disorders. A systematic review of incidence studies by Twelves et al (2003) estimated an incidence of about 17 per 100,000, which varies with different estimates of the proportion of the population with undiagnosed PD. Peak incidence generally occurs between 70 and 79 years of age. The authors report that there is conflicting evidence of an increased incidence in men. The European prevalence for persons 65 years and older is 1.8 (per 100 persons, Just & Ostergaard 2002). It has also been reported that incidence of PD increases with the age of the patient, doubling from 75–79 years and 80–84 years (Twelves et al 2003).

Guttman et al (2003) reported an average annual crude prevalence rate for men between the ages of 25 and 59 of 0.41/1,000 and for those over age 60 of 14.63/1,000. For women, the corresponding figures were 0.30/1,000 and 11.21/1,000. In Australia, the incidence and prevalence of Parkinson's disease is estimated to be 85 and 289 per 100,000, respectively (Mathers et al 1999).

Although PD is the most common neurodegenerative disease, international criteria limit the proportion of patients with late-stage PD who are recommended to benefit from STN DBS (Defer et al 1999). Patients with late-stage PD who have disabling motor fluctuations and good cognitive and general status are thought most likely to benefit from the procedure (Limousin et al 1998). Capecci et al (2005) estimated that less than 10 per cent of all PD patients consecutively referred to their movement disorder centre between July 2000 and July 2002 and 13 per cent of those with disease-related disability were eligible for STN DBS. They reported that advanced age, dementia and concurrent illness were the most common causes of exclusion.

DBS has replaced ablative surgery in Australia as the intervention of choice for patients with late-stage PD who have disabling motor symptoms and no co-morbidities such as dementia.

Figure 1 below presents the HIC data for MBS Item 40851-Bilaterial Implantation of Electrodes, according to the age and gender breakdown for the last financial year.

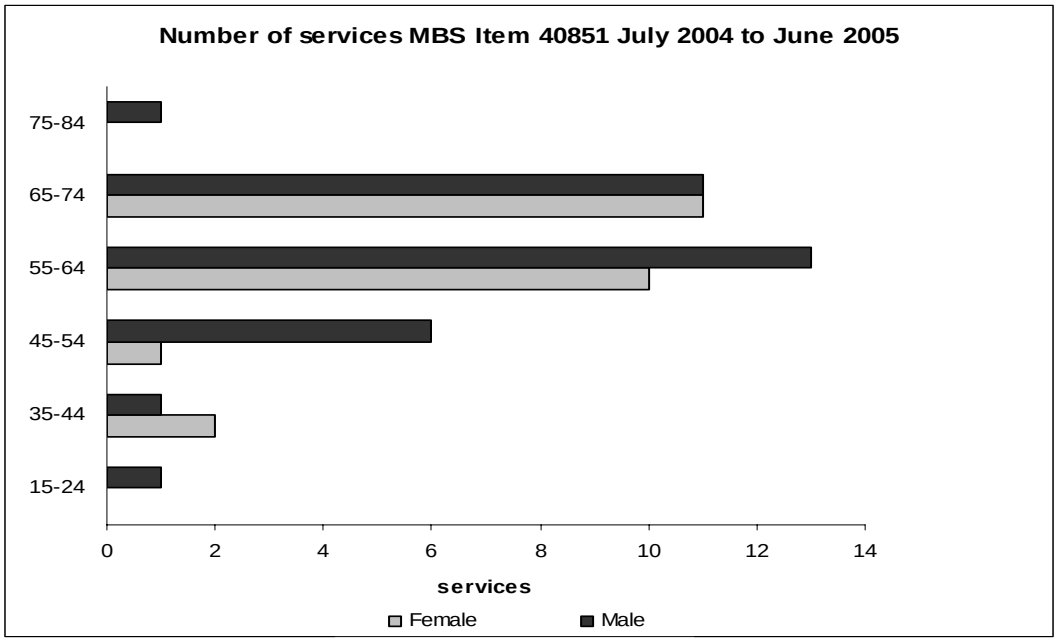

Figure 1 Bilateral implantation of electrodes by age and gender, 2004-05

Data for the 2004-05 financial year (Figure 1) show that 57 males received bilateral implantation of electrodes compared to 33 females, and received them at both a younger and older age. Although as the numbers reported are small this may not be typical for future years. Most patients underwent surgery for DBS between the ages of 55 and 74 years.

Tables 33 and 34 present the number of services and the total benefit that have been provided under the MBS since the introduction of interim funding arrangements for DBS.

Table 33 Total number of services for DBS-relevant MBS items

Financial year	MBS item								Total
	40850 (n)	40851 (n)	40852[a] (n)	40854 (n)	40856 (n)	40858 (n)	40860 (n)	40862 (n)	(n)
2001–2002	11	0	10	0	1	2	9	67	100
2002–2003	49	0	42	4	9	3	46	422	575
2003–2004	10	37	75	10	6	8	65	440	651
2004–2005	13	57	100	24	24	13	120	851	1,202
Total	83	94	227	38	40	26	240	1,780	2,528

[a] Includes patients who received an IPG for conditions other than PD and for re-implantations

Table 34 Total benefit for DBS-relevant MBS items

Financial Year	MBS item								Total
	40850 ($)	40851 ($)	40852 ($)	40854 ($)	40856 ($)	40858 ($)	40860 ($)	40862 ($)	($)
2001–2002	12,091		1,213		38	468	9,000	7,864	30,674
2002–2003	52,496		6,190	800	1,122	952	45,090	47,930	154,580
2003–2004	13,977	90,383	10,041	2,355	628	1,957	63,561	55,990	238,891
2004–2005	18,389	142,085	14,486	4,311	2,819	3,603	120,439	101,008	407,141
Total	96,953	232,468	31,930	7,466	4,607	6,981	238,090	212,792	831,285

Demand as represented by the total number of service has increased each year (Table 33). Given the nature of DBS, this increase may be due to DBS having replaced ablative surgery as the intervention of choice, rather than to an overall increased demand. The annual expenditure on DBS for the 2004-05 financial year was $407,141 and the total expenditure since interim funding was approved is $831,285. Based on data from the UK, the cost to Australia of PD is approximately $73 million per year, comprising 70 per cent hospital care, 14 per cent primary care and 16 per cent pharmacotherapy (MSAC 2001).

Conclusions

The estimate of the costs of the STN DBS procedure under interim MBS funding is $67,475–$73,204 discounted per patient, with potential additional discounted costs of approximately $9,956 as a result of complications of the surgery over five years. The incremental costs are acknowledged to be higher than was estimated in the previous MSAC evaluation (MSAC 2001) because of a change in comparator from ablative surgery to SMT. Ablative surgery and STN DBS have common surgical costs, which resulted in a narrower incremental cost difference.

However, the cost of insertion of an STN DBS system is consistent with the estimate of cost based on data from the UK provided previously of between $60,917 and $75,808 per patient (MSAC 2001). Case series evidence suggests that the insertion of a STN DBS system is likely to result in savings in drug costs of about $57,199 discounted over a five-year period. Other possible cost savings (that could not be quantified) may also be realised as a result of a reduced rate of falls from better control of motor symptoms in patients on DBS compared with those receiving SMT.

Quality of life as an economic variable could not be calculated. The evidence for STN DBS on patient self-reported QoL measures is not straightforward since items measuring physical wellbeing improved significantly at least two years post-surgery but those measuring emotional wellbeing, social support, cognition and communication showed no strong evidence of any improvement.

The extra cost of a 23.7-point improvement in the UPDRS III score is estimated at $20,232–$25,961 if the savings in pharmacotherapy are deducted from the total cost of the procedure, including the costs of complications.

Conclusions

Safety

The safety of DBS for the symptoms of PD was assessed from 42 case series. Findings from these studies indicated the risks associated with DBS, but did not allow quantitation of those risks compared with SMT. While some adverse events were reported to be transient or resolved with treatment, a number were reported to be irreversible.

Nine studies, including a total of 244 participants, reported complications that occurred during surgery. The adverse events reported (and their rates of occurrence in the individual studies) included: ischaemic stroke (4.0%), haemorrhages (2.1–7.1%), haematomas (2.1–12%), confusion (6.9–21.4%) and electrode repositioning/ misplacement of electrodes/lead migration (6.1–14.3%).

Thirty-nine studies, including a total of 791 participants, reported complications that occurred after surgery with a follow-up period of up to 60 months. The hardware-related adverse events reported (and their rates of occurrence in the individual studies) included: electrode and lead problems (1.4–46.0 %) and battery depletion and malfunctions (12.1–84.6 %). Three studies explicitly reported stimulation- and target-related complications, included ballism/chorea, blepharospasms, eyelid apraxia, increased weight and hypophonia.

Irreversible adverse events (and their rates of occurrence in the individual studies) included: weight gain (33.3–87.9%), cognitive changes and increased parkinsonian symptoms (8.0%), fluctuating cognitive, behavioural and mood disorders (5.0%), psychosis and severe depression (6.5%), dysarthria (4.2%), disabling dyskinesias (4.2%) and apraxia of the eyelid opening (6.3%), leg dysaesthesia (7.1%) and ataxia (7.1%), hallucinations (10.2%), dementia (6.1%) and apathy (14.3%), worsening or development of dysphagia (11.1%), depression (6.7%), hypophonia (36.4%) and limb dystonia (3.0%), confusion (11.9%) and intracerebral haemorrhage (1.8%).

Whilst these adverse events were reported to be irreversible, some, for example weight gain, would not require cessation of treatment. In fact, expert opinion suggests that weight gain may be a desirable outcome since weight loss is common in advanced PD. In addition, the reported adverse events may be reversible upon cessation of stimulation.

The assessment of the safety of DBS for the treatment of symptoms of PD was limited by follow-up of the hardware to a maximum of only 60 months. The comparative safety of DBS and SMT is unknown.

Expert opinion suggests that DBS is no less safe, and probably safer, than ablative surgery. Complications arising from DBS tend to be hardware associated rather than neurologic.

Effectiveness

The effectiveness of DBS for the treatment of symptoms of PD was assessed from one double-blind crossover and three case-control studies. DBS appears to be effective for

the treatment of PD symptoms, with statistically significant changes in UPDRS and PDQ-39SI scores observed between case and control participants. Two studies reported statistically significant reductions in UPDRS III scores with stimulation on in the absence of medical therapy. These results therefore show that DBS can ameliorate the symptoms of PD by smoothing out the motor fluctuations and avoiding severe ON periods affected by dyskinesia and severe OFF periods during which the patient experiences the symptoms of PD such as tremor, rigidity and akinesia.

Two case-control studies reported significant reductions in the daily OFF rate (during which medication is not effective) due to DBS. The three case-control studies indicated that DBS also reduced the LEDDs required to maintain control of the symptoms of PD. This reduction may also significantly decrease some of the side effects associated with prolonged high-dose levodopa treatment. However, the assessment of the effectiveness of DBS for the treatment of symptoms of PD was limited by the following:

- the relatively small number of individuals who have been analysed;
- significant losses to follow-up in some studies; and
- follow-up of participants to a maximum of only 48 months in the studies.

Nevertheless, the data reported from these studies are supported by those in the systematic review of the case series literature that included 38 individual studies and up to 471 participants. The review indicated that DBS allowed the maintenance of abilities to perform activities and increased motor function in the absence of SMT.

In addition, patients receiving DBS were found to maintain their ability to perform activities of daily living and increase motor functions over time on lower LEDDs. Whilst the magnitude of this effect attributable to DBS is difficult to quantitate due to a lack of a comparator group in the studies included in the published review, the results reported in the double-blind crossover and case-control studies support the suggestion that the effects were attributable to DBS.

Cost-effectiveness

It has been estimated that the costs of the STN DBS procedure under interim MBS funding is approximately $67,475–$73,204 discounted per patient, with potential additional discounted costs of about $9,956 as a result of complications of the surgery over five years. This cost includes the direct costs of surgery (hardware, the procedure, post-operative monitoring, in-patient stay and procedure- and hardware-related adverse events). This cost may be slightly underestimated as there may be some variability between surgical centres in the extent to which psychological testing is included in the pre-surgery workup. The three-case control studies all reported reductions in the LEDD.

Using case series data as the basis, this reduction in pharmacotherapy is estimated to result in savings in drug costs in the order of $57,199 discounted over a five-year period. Other possible cost savings (that could not be quantified) may also be realised as a result of a reduced rate of falls from better control of motor symptoms in patients on DBS compared with those receiving SMT.

Quality of life as an economic variable could not be calculated. The evidence for STN DBS on patient self-reported QoL measures is not straightforward since items measuring physical wellbeing improved significantly at least two years post-surgery but those measuring emotional wellbeing, social support, cognition and communication showed no strong evidence of any improvement.

The extra cost of a 23.7-point improvement in the UPDRS III score is estimated at $20,232–$25,961 if the savings in pharmacotherapy are deducted from the total cost of the procedure, including the costs of complications.

Readers are advised that the MSAC recommendation in the current report is dependent on the results presented in the current assessment report and those in the previous MSAC report assessing the safety, effectiveness and cost-effectiveness of DBS (MSAC 2001). The MSAC 2001 report can be accessed via: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1031-1/$FILE/msac1031.pdf.

Recommendation

MSAC has considered the safety, effectiveness and cost-effectiveness of deep brain stimulation for refractory severe Parkinson's disease compared with optimal medical therapy.

MSAC finds that there is sufficient evidence of safety and effectiveness, and robust information on cost-effectiveness is unlikely to emerge but the total cost is acceptable for patients in whom other therapies are insufficient.

MSAC recommends that public funding be provided for patients with Parkinson's disease where their response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations.

The Minister for Health and Ageing accepted this recommendation on 24 August 2006.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;

- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;

- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and

- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Kwun Gong	thoracic medicine
Dr Debra Graves	pathology
Professor Jane Hall	health economics
Professor John Horvath	medical advisor to the Department and Health Minister
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Dr Ray Kirk	health research
Associate Professor Donald Perry-Keene	endocrinology
Dr Ewa Piejko	general practice
Mrs Sheila Rimmer	consumer representative
Ms Samantha Robertson	Medicare Benefits Branch
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory Panel

Advisory Panel for MSAC application 1092
Deep brain stimulation for the symptoms of Parkinson's disease

Professor Brendon Kearney (Chair) MBBS, FRACP, FRACMA Executive Director Clinical Systems Department of Human Services	MSAC Member
Mr Raymond Cook MBBS (Hons) FRACS Visiting Medical Officer in Neurosurgery North Sydney Area Health Service Sydney	Royal Australian College of Surgeons nominee
Ms Valerie McKeown Dip Pastoral Ministry, Dip Management (Community Services) South Australian Consumer Representatives Network	Consumers' Health Forum of Australia nominee
Professor Philip Thompson MBBS PhD FRACP Professor of Neurology University Department of Medicine, University of Adelaide Head, Department of Neurology, Royal Adelaide Hospital	Australian Association of Neurologists nominee
Dr Barry I Vieira MBBS FRACP Clinical Head of Service Rehabilitation and Aged Care Osborne Park Hospital Program Director Rehabilitation and Aged Care Unit Joondalup Health Campus	Australian Society for Geriatric Medicine nominee

Evaluators

Monash Evaluation Group Evaluators	Monash University

Department of Health and Ageing

Ms Alex Lloyd Project Manager	Health Technology Section

Appendix C Search strategies

Table C1 Search strategy for OVID databases (Medline, All EBM, CINAHL and Biological Abstracts)

Number	Search term
1	Parkinson Disease/
2	Parkinson$.tw.
3	PD.tw.
4	or/1-3
5	Deep Brain Stimulation/
6	deep brain stimul$.tw.
7	(STN adj DBS).tw.
8	or/5-7
9	exp subthalamus/
10	Globus Pallidus/
11	Pallid$.tw.
12	Sub-thalamic.tw.
13	Subthalamic.tw.
14	or/9-13
15	DBS.tw.
16	exp Electric Stimulation Therapy/
17	Electric stimulation/
18	(electric$ adj stimulat$).tw.
19	Electrodes, implanted/
20	Microelectrodes/
21	stimulat$.tw.
22	(implant$ adj electrode$).tw.
23	brain stimul$.tw.
24	neurostimul$.tw.
25	or/15-24
26	14 and 25
27	8 or 26
28	exp Antiparkinson Agents/
29	LEVODOPA/
30	Dopamine Agonists/
31	exp Cholinergic Antagonists/
32	(Cholinergic adj2 Antagonist$).tw.
33	AMANTADINE/
34	MAO type B inhibitors.mp.
35	exp Monoamine Oxidase Inhibitors/
36	COMT inhibitor$.mp.
37	Catechol O-Methyltransferase/
38	catechol-O-methyltransferase inhibitor$.tw.
39	or/28-38
40	placebo effect/

Table C1 (cont'd) Search strategy for OVID databases (Medline, All EBM, CINAHL and Biological Abstracts)

Number	Search term
41	off.mp.
42	or/40-41
43	or/39,42
44	4 and 27
45	43 and 44
46	limit 45 to yr="2002 - 2005"
47	from 46 keep 1-199
48	from 46 keep 200-249

$=truncation symbol to represent a series of letters at the end of a word segment.
( )= nested terms to be searched together.
adj=terms must be close to one another in the record.
.mp = textword, keyword in the text of the title, abstract or subject heading fields
TEST TERM/=[MeSH] Medical Subject Headings, Medline's subject descriptors
and/or=Boolean operators "AND" and "OR"

Search strategy for Embase

(('globus pallidus'/exp) OR ('subthalamic nucleus'/exp) OR (subthalam*) OR (thalam*) OR (pallidus)) AND (('parkinson disease'/exp) OR (pd)) AND (('brain depth stimulation'/exp) OR (stn AND dbs) OR ('electrostimulation') OR (electrode) OR ('microelectrode'/exp)) AND [humans]/lim AND ([adult]/lim OR [aged]/lim) AND [2002-2005]/py

Search strategy for Australasian Medical Index

((deep brain stimulation) OR (dbs))AND (parkinson*) AND (PY=2002-2005)

Appendix D Internet sites searched

HTA websites

Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
http://www.ccohta.ca/ [Accessed 16 August 2005]

EUROSCAN: The European Information Network on New and Changing Health Technologies
http://www.mrw.interscience.wiley.com/cochrane/cochrane_clhta_articles_fs.html [Accessed 16 August 2005]

HSTAT : Health Services/Technology Assessment Text
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat [Accessed 16 August 2005]

Health Technology Assessment (HTA) Database
http://www.mrw.interscience.wiley.com/cochrane/cochrane_clhta_articles_fs.html [Accessed 16 August 2005]

Institute for Clinical Systems Improvement (ICSI)
http://www.icsi.org/index.asp [Accessed 16 August 2005]

International Network of Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org/ [Accessed 16 August 2005]

The National Coordinating Centre for Health Technology Assessment (NCCHTA)
http://www.hta.nhsweb.nhs.uk/ and http://www.hta.nhsweb.nhs.uk/rapidhta [Accessed 16 August 2005]

National Institute for Clinical Excellence (NICE)
http://www.nice.org.uk/Cat.asp?pn=professional&cn=toplevel&ln=en [Accessed 16 August 2005]

Health Technology Assessment International (HTAi)
http://www.htai.org/ [Accessed 16 August 2005]

Economic evaluation databases

NHS Economic evaluation database
http://www.york.ac.uk/inst/crd/crddatabases.htm [Accessed 16 August 2005]

Health Economics Evaluation Database (HEED), Office of Health Economics
http://dmoz.org/Business/Healthcare/Economics/ [Accessed 16 August 2005]

Health Economics, Policy and Medical Outcomes Sources. Databases and Health Economics Web Sites
http://www.exit109.com/~zaweb/pjp/econ.htm [Accessed 16 August 2005]

Clinical trial registries

CentreWatch clinical trials listing service
http://www.centerwatch.com/ [Accessed 16 August 2005]

ClinicalTrials.com
http://www.clinicaltrials.com/ [Accessed 16 August 2005]

ClinicalTrials.gov
http://www.clinicaltrials.gov/ [Accessed 16 August 2005]

Current Controlled Trials
http://www.controlled-trials.com/ [Accessed 16 August 2005]

NHMRC Clinical Trials Centre
http://www.ctc.usyd.edu.au/trials/registry/registry.htm [Accessed 16 August 2005]

Society for Clinical Trials
http://www.sctweb.org/ [Accessed 16 August 2005]

TrialsCentral
http://www.trialscentral.org/ [Accessed 16 August 2005]

UK The National Research Register
http://www.update-software.com/national/ [Accessed 16 August 2005]

Other relevant websites

US Food and Drug Administration (FDA)
http://www.fda.gov/ [Accessed 16 August 2005]

The National Research Register
http://www.nrr.nhs.uk/ [Accessed 16 August 2005]

Medical Research Council UK
http://www.mrc.ac.uk/ [Accessed 16 August 2005]

National Parkinson's Foundation
http://www.parkinson.org/site/pp.asp?c=9dJFJLPwB&b=71117 [Accessed 16 August 2005]

Appendix E Data from the Australian setting

Results of assessment

The five Australian case series critically appraised in this assessment report are Iansek et al (2002), North Shore Private Hospital/Silberstein et al (2005, unpublished), Silburn and Coyne (2004, unpublished)/Coyne et al (2005, unpublished), O'Sullivan (2004, unpublished) and Mastaglia (2005, unpublished).

Iansek et al (2002) conducted a study of STN DBS in PD at Kingston Centre in Melbourne.

Mastaglia (2005) reported on a study conducted in Perth that examined unilateral and bilateral GPi DBS in PD.

The North Shore Private Hospital study in Sydney reported a retrospective audit of nine individuals undergoing bilateral STN DBS for the treatment of PD from July 2003 to August 2004. An update of this information was provided by Silberstein et al (2005), including 16 additional patients treated to July 2005.

O'Sullivan (2004) reported on a study conducted in Sydney that examined bilateral STN DBS in PD.

Silburn and Coyne (2004) examined STN DBS in 47 individuals with PD at Wesley and St Andrew Hospitals in Brisbane. Coyne et al (2005) updated this information, including 58 additional patients treated at Wesley and St Andrew Hospitals in Brisbane and North Shore Private Hospital in Sydney. It is unclear if there was double reporting in Coyne et al (2005) and North Shore Private Hospital (2004)/Silberstein et al (2005).

Characteristics of case series

Table E1 presents the descriptive characteristics of the four included case series assessing the safety and efficacy of STN DBS and the one case series assessing the safety and efficacy of GPi DBS (Mastaglia 2005).

Three of the four STN DBS case series (Iansek et al 2002, North Shore Private Hospital/Silberstein et al 2005, Silburn & Coyne 2004/Coyne et al 2005) reported consecutive case series, including one retrospective cohort (North Shore Private Hospital/Silberstein et al 2005), and one study was a selected case series (O'Sullivan 2004). The largest of these was a consecutive case series of 47/58 patients (Silburn & Coyne 2004/Coyne et al 2005) and the smallest was a selected case series describing results from 7/36 patients who underwent surgery (O'Sullivan 2004). All studies involved PD patients from 36 to 74 years of age and follow-up after the STN DBS procedure ranged from one week to seven years. Three of the studies (Iansek et al 2002, North Shore Private Hospital/Silberstein et al 2005, O'Sullivan 2004) were partly or fully funded by Medtronic Australasia. The source of funding was not reported in Silburn and Coyne (2004)/Coyne et al (2005).

Table E1 Characteristics of the Australian studies

Study & centre	Study design (NHMRC level of evidence)	Sample	Inclusion criteria	Exclusion criteria	Follow-up
Iansek et al (2002) Melbourne Kingston Centre	Prospective cohort/consecutive case series (Level IV)	14 patients enrolled 1996–2000 9 males Median age: 59 years Range: 36–74 years	Idiopathic PD, age <75 years, intact cognition with no psychotic side effects to medications or past history, good motor response to medication, refractory motor fluctuations	Significant comorbidity, age >75 years, those with psychotic side effects to medication or past psychiatric history	Up to 12 months Data reported for 6 months' follow-up
Mastaglia (2005) Perth Australian Neuromuscular Research Institute, Queen Elizabeth II Medical Centre	Case series (Level IV)	20 patients: 9 unilateral GPi DBS 11 bilateral GPi DBS	Levodopa responsivity (>30% reduction in motor component of UPDRS) Symptoms of PD refractory to optimal medical interventions (dyskinesia, intractable tremor, marked on/off fluctuations) <70 years Medically fit Able to undergo MRI Nil dementia, psychiatric or cognitive impairment Ability to give informed consent	Not reported	Mean: 35 months
North Shore Private Hospital, (2004) Sydney	Retrospective audit/consecutive case series (Level IV)	9 patients enrolled Jul 2003–Aug 2004 Mean age: 54 years Range: 45–69	PD (inclusion criteria not stated clearly)	Atypical parkinsonian features	Time to post-operative assessment : Mean: 4 months Range: 0.33–13
Silberstein et al (2005) North Shore Private Hospital Sydney	Consecutive case series (Level IV)	25 patients enrolled Jul 2003–Jul 2005 15 males Mean age: 56 years Range: 42–69 Mean duration of PD: 11 years Range: 5–25	PD patients demonstrating significant responsiveness to a formal levodopa test and a clear understanding of the potential risks and benefits of the procedure	Significant cerebral atrophy or structural cerebral pathology as determined by cerebral MRI Substantive psychiatric or behavioural co-morbidity Cognitive decline Non levodopa responsive symptomology – eg ON gait freezing Major general medical co-morbidity	Time to follow-up after initial DBS procedure: Mean: 9.5 months Range: 0.75–23

Table E1 (cont'd) Characteristics of the Australian studies

Study & centre	Study design (NHMRC level of evidence)	Sample	Inclusion criteria	Exclusion criteria	Follow-up
O'Sullivan (2004) Sydney	Selected case series (Level IV)	Surgery performed on 36 patients (1997–2004) but only 7 patients followed up Mean age±SD for 7 patients: 61.4±7.4 years	Patients with PD of duration longer than 2 years and who had the STN DBS procedure more than 2 years ago	Not specified	Time to follow-up: Mean: 49 months Range: 25–85
Silburn & Coyne (2004) Wesley Hospital and ST Andrew Hospital Brisbane	Consecutive case series (Level IV)	47 patients 33 males Mean age±SD: 60±9 years Range: 40–74	PD patients where medication is no longer sufficient to maintain quality of life such that motor fluctuations impact on function or become socially intrusive. In particular, sudden unpredictable and prolonged OFF periods and drug-induced dyskinesia	Uncontrolled medical problems, eg bleeding diathesis, unstable angina, major depressive disorders, non drug-related psycho-affective disorders and dementia	Mean±SD: 10±6 months
Coyne et al (2005) Wesley Hospital, St Andrew Hospital & North Shore Private Hospital[a] Brisbane and Sydney	Consecutive case series (Level IV)	58 patients	Not reported, assume as above	Not reported, assume as above	Mean±SD: 10±6 months

Parkin et al (2002) also conducted a multi-centre study (Radcliffe Infirmary-Oxford, Charing Cross, London and Princess Alexandra Hospital, Brisbane) of unilateral and bilateral pallidotomy in a consecutive case series of 115 patients with PD. Approximately 50 of these patients were from Australia

[a] It is unclear if there is some double reporting of patients treated in North Shore Private in North Shore Private Hospital (2004) and Silberstein et al (2005)

The included case series by Mastaglia (2005) included 20 patients undergoing GPi DBS, however the age of the patients undergoing the procedure was not reported. Patients in this study were followed up for a mean of 9.5 (range: 0.75-23) months. The source of funding was not reported in Mastaglia (2005).

The intervention, comparison and outcomes measured in the included cases series are compiled in Table E2. In four studies (Iansek 2002, North Shore Private Hospital 2004/Silberstein et al 2005, Silburn & Coyne 2004/Coyne et al 2005, O'Sullivan 2004), the intervention was STN DBS and in one study the intervention was GPi DBS (Mastaglia 2005) in PD. The comparator varied across the studies, but involved medication (ON or OFF) and/or stimulation (ON or OFF).

Table E2 Characteristics of intervention, comparators and outcome measures in the included Australian studies

Study & centre	Study design (NHMRC level of evidence)	Sample	Intervention	Comparison	Outcome measure
Iansek et al (2002) Kingston Centre Melbourne	Prospective cohort/ consecutive case series (Level IV)	14 patients enrolled 1996–2000 9 Males Median age: 59 years Range: 36–74	Bilateral STN DBS	Pre-surgery: Medication on and off Post-surgery at 1, 3, 6, 12 months: . meds on–stim off . meds on–stim on . meds off–stim off . meds off–stim on	UPDRS Gait parameters Psychiatric evaluation Neuropsychometric testing
Mastaglia (2005) Australian Neuromuscular Research Institute, Queen Elizabeth II Medical Centre Perth	Case series (Level IV)	20 patients: 9 unilateral GPi DBS 11 bilateral GPi DBS	Bilateral and unilateral GPi DBS	Scores taken from change in pre- to post-operative values of UPDRS part III and AIMS and both ON and OFF medical states assessed	Motor: UPDRS III scores and subscores Dyskinesias: Abnormal Involuntary Movement Scale (AIMS) UPDRS IVa Clinical Global Impression
North Shore private hospital Sydney	Retrospective audit/ consecutive case series (Level IV)	9 patients enrolled Jul 2003–Aug 2004 Mean age: 54 years Range: 45–69	STN DBS	Pre-surgery: Medication on and off Post-surgery: . meds on–stim off . meds on–stim on . meds off–stim off . meds off–stim on	UPDRS motor score LEDD Adverse events
Silberstein et al (2005) North Shore Private Hospital Sydney	Consecutive case series (Level IV)	25 patients enrolled Jul 2003–Jul 2005 15 males Mean age: 56 years Range: 42–69 Mean duration of PD: 11 years Range: 5–25	STN DBS	Pre-surgery: Medication on and off Post-surgery: . meds on–stim off . meds on–stim on . meds off–stim off . meds off–stim on	UPDRS (post-operative alteration in performance of activities of daily living, motor performance, daily OFF time) Alteration in medication dose Adverse events

Table E2 (cont'd) Characteristics of intervention, comparators and outcome measures in the included Australian studies

Study/Centre	Study design (NHMRC Level of evidence)	Sample	Intervention	Comparison	Outcome measure
O'Sullivan (2004) Sydney	Selected case series (Level IV)	Surgery performed on 36 patients (1997–2004) but only 7 patients followed up Mean age±SD for 7 patients: 61.4±7.4 years	STN DBS	Pre-surgery: Medication on and off Post surgery: . meds on and off	Post-operative complications
Silburn & Coyne (2004) Wesley Hospital & St Andrew Hospital Brisbane	Consecutive case series (Level IV)	47 patients 33 males Mean age±SD: 60±9 years Range: 40–74	STN DBS	Pre-surgery: Medication on Post-surgery: . meds on–stim on	UPDRS LEDD
Coyne et al (2005) Wesley Hospital, St Andrew Hospital and North Shore Private Hospital [a] Brisbane and Sydney	Consecutive case series (Level IV)	58 patients	STN DBS	Pre-surgery: Medication on Post-surgery: . meds on–stim on . meds off–stim on	UPDRS LEDD Surgical complications

[a] It is unclear if there is some double reporting of patients treated in North Shore Private Hospital as reported in North Shore Private Hospital (2004) and Silberstein et al (2005)

Validity of the case series

Relevant patient inclusion and exclusion criteria in these studies are presented in Table E1. All of the appraised studies described the included participants explicitly. The exclusion criteria were not clearly stated in two studies (Mastaglia 2005, O'Sullivan 2004). In all of the studies, it is unlikely that all of the participants entered into the studies at a similar stage of PD. Although surgery was performed on 36 patients in the study of O'Sullivan (2004), all of the participants were not included and only seven patients were followed.

Of the four included studies, only O'Sullivan (2004) demonstrated sufficient patient follow-up. The description of the DBS technique was explicit in all of the studies and outcomes were assessed objectively.

Is it safe?

Complications arise from both the surgical procedure for STN DBS and also as a consequence of the stimulation. Three of the five studies reported a need to reposition the electrodes in some patients. Another study reported that some patients had developed infection to either the pacemaker box or the extension wires going towards the brain. In such cases, the pacemaker box or extension wires were removed and replaced after complete recovery from the infection three months later. Some patients experienced confusion as a result of surgery and there were two cases of urinary tract infection that were also considered to be minor complications of surgery.

The major complications relating to surgery were two cases of cerebral haemorrhage, one of which left the patient with significant cognitive sequelae necessitating supervised care and the other resulted in death of the patient from intracerebral haemorrhage three weeks after the procedure. In relation to complications associated with stimulation, there were several reports of patients experiencing dysarthria and hypophonia and, to a lesser degree, emotional lability. Two patients died due to progression of the disease with death occurring post-operatively at six months and five years, respectively. There was one patient death for which the cause was unclear.

Is it effective?

Table E3 lists outcomes measured used in the included studies. Four of the five studies reported that the improvement of UPDRS motor scores in response to stimulation was less than that to medication pre-operatively (Iansek 2002, Mastaglia 2005, North Shore Private Hospital 2004/Silberstein et al 2005, O'Sullivan 2004). The largest study, conducted by Silburn and Coyne (2004)/Coyne et al (2005), did not include measurements in the absence of medication or stimulation post-operatively, therefore a suitable comparator does not exist for this case series.

The five case series collected in the Australian setting varied in follow-up time after the STN DBS procedure from one week to seven years. As a result, there is limited robust evidence in the Australian setting reporting the effectiveness of long-term STN DBS compared to SMT in PD patients. The results from the Australian case series are, however, consistent with findings from the double-blind crossover study and case-control studies that have been included in the current review and those reported in a published systematic review of the large body of evidence of international case series.

In particular, results reported for the 25 patients undergoing STN DBS at North shore Private Hospital (Silberstein et al 2005), reported UPDRS II and III scores before and after surgery in the OFF-medication state with stimulation ON. Silberstein et al (2005) reported that the mean±standard error of the mean (SEM) UPDRS II score OFF medication at baseline was 49±1.6 points, decreasing to 25.2±2.5 points at last follow-up. This reduction in the UPDRS II scores represents an increase in the ability of the participants to undertake activities of daily living. Similarly, the authors reported that the UPDRS III scores OFF medication at baseline was 23.3±1.6 points, decreasing to 11.1±1.6 points at last follow-up. This reduction in the UPDRS III scores represents an improvement in motor control. These results suggest that DBS is effective in increasing the ability of individuals with PD to perform activities of daily living and in maintaining motor control in the absence of medication.

Mastaglia (2005), and Silburn & Coyne (2004)/Coyne (2005) also reported improvements in UPDRS IV. The UPDRS IV score provides information about the complications of therapy, in particular to medication when a smooth and sustained response to medication is no longer provided and disabling dyskinesias are experienced.

Mastaglia (2005) reported that post-operative dyskinesias decreased by 76 per cent at up to 35 months of follow-up and Silburn & Coyne (2004)/Coyne (2005) reported mean improvement of 88 per cent in UPDRS IV scores post-operatively, a statistically significant difference from pre-operative scores ($p<0.0005$). Iansek et al (2002) also reported an improvement in levodopa-induced dyskinesia (UPDRS IV); however the improvement did not reach statistical significance due to several participants not presenting with dyskinesias.

Table E3 Outcomes measured in the included Australian studies

Study	Type and size of study and period of follow-up	Reduction in fluctuations in motor function, length of time in OFF state, OFF period dystonia with stimulation?	Improvement in OFF period UPDRS scores with stimulation? Improvement in UPDRS score with stimulation when levodopa is not effective		Improvement in ON medication dyskinesia and UPDRS scores with stimulation? Improvement in UPDRS score with stimulation		LEDD reduced? Yes/No	Improvement in OFF period cardinal symptoms: UPDRS scores for rigidity, tremor, gait, Schwab & England, Hoehn & Yahr scales with stimulation
		Reduced motor fluctuations	OFF motor score (UPDRS III)	OFF ADL score (UPDRS II)	ON motor score (UPDRS III)	Levodopa-induced dyskinesia (UPDRS IV)	LEDD (% reduction)	OFF cardinal symptoms improve
Iansek (2002) Kingston Centre Melbourne	STN DBS=14 Follow-up for 10/14	Not reported	Yes Mean improvement at 6 months (versus pre-surgery): $t_9 = 5.952$, $p<0.001$	Not reported	Yes Mean improvement at 6 months (versus pre-surgery): $t_9 = 4.291$, $p=0.002$	Yes Not significant as several patients had no presenting dyskinesia	Yes At last follow-up mean reduction = 30%	Yes Mean improvement (versus pre-surgery): Stride length:$T_6=3.175$, $p=0.019$; Velocity$T_6=3.625$, $p=0.011$
Mastaglia (2005) Australian Neuromuscular Research Institute, Queen Elizabeth II Medical Centre Perth	GPi DBS	Not reported	Yes At a mean of 7 months post-operatively, bilateral GPi DBS reduced scores by a mean of 46% in the OFF period and unilateral GPi DBS reduced scores by a mean of 18% in the OFF period	Not reported	Yes. At a mean of 7 months post-operatively, bilateral GPi DBS reduced scores by a mean of 18% in the ON period	Yes At a mean of 7 months post-operatively, dyskinesias decreased by 76% in uni- and bi-lateral stimulation groups and were maintained at mean follow-up of 35 months	No significant change in medication therapy identified post-operatively	Not reported

Table E3 (cont'd) Outcomes measured in the included Australian studies

Study	Type and size of study and period of follow-up	Reduction in fluctuations in motor function, length of time in OFF state, OFF period dystonia with stimulation?	Improvement in OFF period UPDRS scores with stimulation? Improvement in UPDRS score with stimulation when levodopa is not effective		Improvement in ON medication dyskinesia and UPDRS scores with stimulation? Improvement in UPDRS score with stimulation		LEDD reduced? Yes/No	Improvement in OFF period cardinal symptoms: UPDRS scores for rigidity, tremor, gait, Schwab & England, Hoehn & Yahr scales with stimulation
		Reduced motor fluctuations	OFF motor score (UPDRS III)	OFF ADL score (UPDRS II)	ON motor score (UPDRS III)	Levodopa-induced dyskinesia (UPDRS IV)	LEDD (% reduction)	OFF cardinal symptoms improve
North Shore Private Hospital Sydney	STN DBS n=9 at last follow-up Mean follow-up at: 4 months Range: 0.33–13	Not reported	Yes. Mean improvement at last follow-up (versus pre-surgery): 52.6%, p<0.001	Not reported	Not reported	Not reported	Yes Mean improvement (versus pre-surgery) at last follow-up: 82%, p<0.001	Not reported
Silberstein et al (2005) North Shore Private Hospital Sydney	STN DBS n=25 at last follow-up Mean follow-up at: 9.5 months Range: 0.75–23	Not reported	Yes Mean±SEM pre-operatively off medication: 49±1.6 Mean±SEM post-operatively off medication: 25.2±2.5 Relative improvement in mean±SEM: 49.4±4.5%, p<0.001	Yes Mean±SEM pre-operatively off medication: 23.3±1.6 Mean±SEM post-operatively off medication: 11.1±1.6 Relative improvement in mean±SEM: 49.9±6.8%, p<0.001	No. Mild worsening (versus pre-surgery on medication) at last follow-up: Mean±SEM pre-operatively on medication: 17.7±2.2 Mean±SEM post-operatively on medication: 22±1.3, p=0.04	Not reported	Yes Mean±SEM pre-operatively: 1,833±254 mg Mean±SEM post-operatively: 599±175 mg Mean±SEM reduction: 65±12%, p<0.001 35% of patients no longer required medication	Not reported

Table E3 (cont'd) Outcomes measured in the included Australian studies

Study	Type and size of study and period of follow-up	Reduction in fluctuations in motor function, length of time in OFF state, OFF period dystonia with stimulation?	Improvement in OFF period UPDRS scores with stimulation? Improvement in UPDRS score with stimulation when levodopa is not effective		Improvement in ON medication dyskinesia and UPDRS scores with stimulation? Improvement in UPDRS score with stimulation		LEDD reduced? Yes/No	Improvement in OFF period cardinal symptoms: UPDRS scores for rigidity, tremor, gait, Schwab & England, Hoehn & Yahr scales with stimulation
		Reduced motor fluctuations	OFF motor score (UPDRS III)	OFF ADL score (UPDRS II)	ON motor score (UPDRS III)	Levodopa-induced dyskinesia (UPDRS IV)	LEDD (% reduction)	OFF cardinal symptoms improve
O'Sullivan (2004) Sydney	STN DBS n=7 at last follow-up Mean follow-up at: 49 months Range: 25–85	Not reported	Yes. Mean improvement at last follow-up(versus pre-surgery): 32.8%, p=0.026	Not reported	Not reported	Not reported	No Mean improvement (versus pre-surgery) at last follow-up: 25.7%, p=0.36	Not reported
Silburn & Coyne (2004) Wesley Hospital and St Andrew Hospital Brisbane	STN DBS n=47 at last follow-up Mean(±SD) follow up at: 10±6 months	Not reported	Not reported	Not reported	Yes. Mean improvement (versus pre-surgery) at last follow-up: 44%, p<0.0005	Yes Mean improvement (versus pre-surgery) at last follow-up: 88%, p<0.0005	Yes Mean improvement (versus pre-surgery) at last follow-up: 68%, p<0.0005 30% of patients no longer required medication	Yes Mean improvement (versus pre surgery) at last follow-up: UPDRS II on medication ADL 38%, p<0.0005
Coyne et al (2005) Wesley Hospital, St Andrew Hospital and North Shore Private Hospital[a] Brisbane and Sydney	STN DBS n 58 at last follow-up Mean(±SD) follow up at: 10±6 months	Not reported	Not reported	Not reported	Yes. Mean improvement (versus pre-surgery) at last follow-up: 52%, p<0.0005	Yes Mean improvement (versus pre-surgery) at last follow-up: 88%, p<0.0005	Yes Mean improvement (versus pre-surgery) at last follow-up: 68%, p<0.0005 30% of patients no longer required medication	Yes Mean improvement (versus pre-surgery) at last follow-up: UPDRS II on medication ADL 38%, p<0.0005

[a] It is unclear if there is some double reporting of patients treated in North Shore Private Hospital as reported in North Shore Private Hospital (2004) and Silberstein et al (2005)

UPDRS III (Motor) scores

Table E4 shows the comparison of UPDRS III scores pre- and post-operatively with and without medication. All five studies used the UPDRS part III to compare motor scores for patients pre- and post- STN DBS and GPi DBS. Paired sample t-tests were used to compare mean UPDRS scores pre- and post-intervention with and without medication and with and without stimulation. Three of the five studies included data that allowed calculation of the percentage improvement in UPDRS part III post-operatively on stimulation alone compared to the pre-operative improvement with medication (Table E4).

Only one study limited the comparison of outcome measures to best ON-medication response before surgery and best ON-medication response with active stimulation post-surgery (Silburn & Coyne 2004). Coyne et al (2005) reported the improvement from best ON-medication pre-operatively compared with best ON-stimulation post-operatively, with or without medication. It is possible to compare results from all four studies based on these measurements. However, these studies did not examine the potential benefits of STN DBS in a drug-free context.

Table E4 Comparison of UPDRS III scores pre- and post-operatively with and without medication in the Australian studies

Study and centre (number enrolled in study)	UPDRS III Motor Scores		
	Improvement of stimulation alone versus pre-operative improvement with medication (%)	Mean pre-operative on medication±SD[a]	Mean post-operative, on medication, on stimulation±SD[a]
Iansek et al (2002) Kingston Centre, Melbourne (n=10)	71	13±8	11±8
Mastaglia 92005) Australian Neuromuscular Research Institute, Queen Elizabeth II Medical Centre, Perth (n=20)	Not reported	Not reported	Not reported
North Shore Private Hospital (2004) Sydney (n=9)	80	16±10	NA
Silberstein et al (2005) North Shore Private Hospital, Sydney (n=25)	Not reported	17.7±2.2 (SEM)	22±1.3 (SEM)
O'Sullivan (2004) Sydney (n=7)	55	26±8	NA
Silburn & Coyne (2004) Wesley Hospital and St Andrew Hospital, Brisbane (n=47)	NA	22±11	13±11
Coyne et al (2005) Wesley Hospital, St Andrew Hospital & North Shore Private Hospital Brisbane & Sydney (n=58)[b]	44 (best ON-medication pre-op compared to best ON-stimulation post-op, with or without medication)	Not reported	Not reported

Abbreviations: NA, not applicable; SD, standard deviation; SEM, standard error of the mean

[a] Unless otherwise stated

[b] It is unclear if there is some double reporting of patients treated in North Shore Private Hospital as reported in North Shore Private Hospital (2004) and Silberstein et al (2005)

Levodopa-equivalent daily dose (LEDD)

Results comparing the LEDD pre-operatively and post-operatively for each patient group are shown in Table E5. LEDD was used to indicate any reduction in anti-parkinsonian drugs for STN DBS and GPi DBS patients after the procedure. For individuals undergoing STN DBS, the reduction in LEDD ranged from 25.7 per cent (O'Sullivan 2004) to 81.8 per cent (North Shore Private hospital 2004). However, results from North Shore Private Hospital showed a smaller reduction in LEDD of 67.3 per cent with the enrolment of additional patients (Silberstein et al 2005). Mastaglia (2005) reported no significant difference in medication therapy for individuals undergoing uni- or bi-lateral GPi DBS. It is noteworthy that two consecutive case series reported that 30 per cent (14/47) (Silburn & Coyne 2004/Coyne et al 2005) and 35 per cent (Silberstein et al 2005) of patients became drug-free after the procedure.

Table E5 Comparison of LEDD pre- and post-operatively in patients with STN DBS in the Australian studies

Study and centre (number enrolled in study)	Pre-operative LEDD (mg)	Mean post-operative LEDD (mg)	Reduction from baseline (%)
Iansek et al (2002) Kingston Centre, Melbourne (n=10)	Mean: 1,417 Range: 400–3,500	Mean: 998 Range: 300–2,280	29.6
Mastaglia 92005) Australian Neuromuscular Research Institute, Queen Elizabeth II Medical Centre, Perth (n=20)	Not reported	Not reported	Reported no significant difference in medication therapy has been identified
North Shore Private Hospital (2004) Sydney (n=9)	Mean: 1,993 Range: 1,020–3,860	Mean: 61 Range:0–800[a]	81.8
Silberstein et al (2005) North Shore Private Hospital, Sydney (n=25)	Mean: 1,833 SEM: 254	Mean: 599 SEM: 175[b]	67.3
O'Sullivan (2004) Sydney (n=7)	Mean: 1,800 Range: 692–4,800	Mean: 1,337 Range: 900–2,060	25.7
Silburn & Coyne (2004) Wesley Hospital and St Andrew Hospital, Brisbane (n=47)	Mean: 1,487 SD: 1,043	Mean: 471 SD: 503[c]	68.3
Coyne et al (2005) Wesley Hospital, St Andrew Hospital & North Shore Private Hospital Brisbane & Sydney (n=58)[b]	Mean: 1,487	Mean: 471[d]	68.3

[a] Reported one patient not receiving any LEDD, although this was less than a week after the procedure
[b] Reported that 35% of patients no longer required medication
[c] It is unclear if there is some double reporting of patients treated in North Shore Private Hospital as reported in North Shore Private Hospital (2004) and Silberstein et al (2005)
[d] Reported that 14 out of 47 patients (30%) became drug-free after the procedure

Conclusions

The five studies from Australia are all case series, which may reveal some information about the usefulness of DBS for symptoms of PD. However, given the lack of data from comparator groups to provide information on the natural progression of the disease and the effect on symptoms over the follow-up period of the studies, it is difficult to quantify how much DBS contributed to the reported improvements in symptoms and reduction in medication.

The results reported from these Australian studies are consistent with the improvements in symptoms and reduction in LEDD observed in the double-blind crossover study and the case-control studies included in the current review, and to the published systematic review of the large body of evidence that exists for DBS in the form of international case series.

Appendix F Studies included in this review

Capecci, M., Ricciuti, R.A. et al, 2005. 'Functional improvement after subthalamic stimulation in Parkinson's disease: A non-equivalent controlled study with 12-24 month follow up', *Journal of Neurology, Neurosurgery &Psychiatry*, 76 (6), 769–774.

Hjort, N., Ostergaard, K. & Dupont, E. 2004. 'Improvement of sleep quality in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus', *Movement Disorders*, 19 (2), 196–199.

Just, H. & Ostergaard, K. 2002. 'Health-related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei', *Movement Disorders*, 17 (3), 539–545.

Rodriguez-Oroz, M.C., Zamarbide, I. et al, 2004. 'Efficacy of deep brain stimulation of the subthalamic nucleus in Parkinson's disease 4 years after surgery: double blind and open label evaluation', *Journal of Neurology, Neurosurgery & Psychiatry*, 75 (10), 1382–1385.

Appendix G Studies excluded from critical appraisal

Case-control study with normal controls

Dauper, J., Peschel, T. et al, 2002. 'Effects of subthalamic nucleus (STN) stimulation on motor cortex excitability', *Neurology*, 59 (5), 700–706.

Maurer, C., Mergner, T. et al, 2003. 'Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease', *Brain*, 126 (Pt 5), 1146–1163.

Sturman, M.M., Vaillancourt, D.E. et al, 2004. 'Effects of subthalamic nucleus stimulation and medication on resting and postural tremor in Parkinson's disease', *Brain*, 127 (Pt 9), 2131–2143.

Results not presented separately for individuals undergoing DBS

Farrell, A., Theodoros, D. et al, 2005. 'Effects of neurosurgical management of Parkinson's disease on speech characteristics and oromotor function', *Journal of Speech, Language, and Hearing Research*, 48 (1), 5–20.

Comparative study of patients with DBS, comparing patients no longer taking medication to those still requiring medication

Valldeoriola, F., Pilleri, M. et al, 2002. 'Bilateral subthalamic stimulation monotherapy in advanced Parkinson's disease: long-term follow-up of patients', *Movement Disorders*, 17 (1), 125–132.

Systematic review of case series of STN DBS only

Hamani, C., Richter, E. et al, 2005. 'Bilateral subthalamic nucleus stimulation for Parkinson's disease: a systematic review of the clinical literature', *Neurosurgery*, 56 (6), 1313–1321.

Not received at time of writing of report

Garcia Ruiz, P.J., Muniz de Igneson, J. et al, 2005. 'Evaluation of timed tests in advanced Parkinsonian patients who were candidates for subthalamic stimulation', *Clinical Neuropharmacology*, 28 (1), 15–17.

Abbreviations

ADL	Activity of Daily Living
AIHW	Australian Institute of Health and Welfare
AR-DRG	Australian Refined - Diagnostic Related Group
BDI	Beck Depression Inventory
B'DS	Brown's Disability Scale
BOD	Burden of disease
CI	confidence interval
DALY	disability adjusted life years
DBS	deep brain stimulation
DRG	Diagnostic Related Group
FIM	Functional Independence Measure
GPi	globus pallidus internus
HIC	Health Insurance Commission
HTA	health technology assessment
Hz	hertz
ICER	incremental cost-effectiveness ratio
IPG	implantable pulse generator
LEDD	levodopa equivalent daily dose
MBS	Medicare Benefit Schedule
PD	Parkinson's disease
PDQ-39SI	Parkinson's Disease Questionnaire Summary Index
QALY	quality affected life years
QoL	quality of life
RCT	randomised controlled trial
SD	standard deviation
SEM	standard error of the mean
SMT	standard medical therapy
STN	subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS III	Unified Parkinson's Disease Rating Scale Motor section
UPDRS-ADL	Unified Parkinson's Disease Rating Scale for Activity of Daily Living
UPDRS-ADL DI	Unified Parkinson's Disease Rating Scale for Activity of Daily Living Disability Items
μs	micro second
V	volts
YLD	Years lived with diability
YLL	Years of life lost

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