Deep brain stimulation for the symptoms of Parkinson's disease

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MSAC application 1031

Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth 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.

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

Contents

Executive summary ..... **vii**

Introduction **1**

Background **2**

Deep brain stimulation for symptoms of Parkinson's disease 2
Clinical need/burden of disease 4
Existing procedures 7
Comparator 7
Marketing status of the device/technology 7
Current reimbursement arrangements 8

Approach to assessment **9**

Review of literature 9
Expert advice 13

Results of assessment **14**

Is it safe? 14
Is it effective? 18
What are the economic considerations? 29

Conclusions **35**

Safety 35
Effectiveness 35
Cost-effectiveness 36

Recommendation **37**

Appendix A MSAC terms of reference and membership **38**

Appendix B Supporting committee **39**

Supporting committee for MSAC Application 1031 - Deep brain stimulation for the symptoms of Parkinson's disease 39

Appendix C Studies included in the review 40

Studies comparing DBS with ablative surgery 40
Studies comparing DBS with medical therapy (medication on/off or stimulation off) 40

Appendix D Staging and rating scales used for Parkinson's disease 41

Hoehn and Yahr Staging of Parkinson's Disease[69] 41
United Parkinson's Disease Rating Scale[70] 41
Frenchay Activities Index[68] 41

Appendix E Conversion to Australian dollars 42

Abbreviations and Definitions 43

References 45

Tables:

Table 1 Prevalence, mortality, disease burden and disease disability data* 5

Table 2 Mortality, years of life lost due to mortality (YLL), years of life lost due to disability (YLD) and disability adjusted life years (DALYs) stratified by age and sex 6

Table 3 TGA Listing and Registration numbers 8

Table 4 Electronic databases including versions used in the review of clinical effectiveness of DBS 9

Table 5 Search terms used to identify citations for clinical effectiveness of DBS9

Table 6 Domains and levels used in the assessment of methodologic quality 12

Table 7 Designation of levels of evidence 13

Table 8 Adverse effects and events associated with stimulation of the Subthalamic Nucleus (STN) 15

Table 9 Adverse effects and events associated with stimulation of the Thalamus (site not specified) 15

Table 10 Adverse effects and events associated with stimulation of the Ventral Intermediate Thalamic Nucleus 16

Table 11 Adverse effects and events associated with stimulation of the Globus Pallidus internus (GPi) 17

Table 12 Descriptive characteristics of RCTs comparing DBS with ablative surgery* 18

Table 13 Methodological quality of included studies comparing DBS with ablative surgery 19

Table 14 Patient criteria of included studies comparing DBS with ablative surgery 20

Table 15 Cost components of DBS, as stated in MSAC application 30

Table 16 UK price tariffs (converted to A$) for unilateral pallidotomy, thalamotomy and DBS (with in-patient follow-up)[a,b] 31

Table 17 Five year costs for ablative surgery (converted from UK costs) 32

Table 18 Five year costs for DBS (converted from UK costs) 32

Table 19 Five year costs for DBS (higher follow-up estimate) (converted from UK costs) 32

Executive summary

The procedure

Deep brain stimulation (DBS) involves the placement of electrical leads into one (unilateral) or both (bilateral) sides of the basal ganglia of the brain. There are currently three targets used for DBS. These are the thalamic nucleus, the sub-thalamic nucleus (STN) and the globus pallidus internus (GPi). Symptoms such as tremor or dyskinesias differentiate 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 patients with Parkinson's disease the key indication for deep brain stimulation is that medical therapy no longer provides a smooth or sustained motor response. Before patients proceed to DBS it is desirable for two neurologists to agree all drug manipulations have been exhausted.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth 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 the Centre for Clinical Effectiveness was engaged to conduct a systematic review of literature on deep brain stimulation for symptoms of Parkinson's disease. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

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

Clinical need

Parkinson's disease is a progressive neurodegenerative disorder. Symptoms include rigidity, tremor, bradykinesia and postural instability. Most patients with the disease are over 50 years of age although at least 10 percent of cases occur earlier. Symptoms and progression of the disease vary between patients, but ultimately significant disability is experienced by many.

In 1996 the incidence of Parkinson's disease in Australia was estimated to be 40 per 100,000 population with a prevalence of 200 per 100,000 population. Costs to the health system for Parkinson's disease for 1993-94 were $149 million (mainly associated with nursing home care). In addition, the number of hospitalisations for Parkinson's disease in the 1997-98 fiscal year was 3,132 patients.

There is a lack of evidence surrounding the proportion of patients with Parkinson's disease that may be considered for neurosurgery although it has been suggested between one and ten percent may be eligible.

Safety

Limited information suggests adverse effects from DBS are generally mild, reversible, and less frequent (often improving when the level of stimulation is reduced) compared to those of ablative surgery (the hallmark being permanence and irreversibility). However, particular adverse effects differed according to target site and no quantitative data are available on incidence.

After six months of follow-up, patients receiving thalamotomy were more likely to experience surgical complications compared to those receiving thalamic stimulation, although sample sizes are too small to warrant statistical analysis. Similar results were found for pallidotomy versus pallidal stimulation.

More serious events such as death and haemorrhage have been associated with DBS. However the majority of the adverse effects presented in the papers were short-term outcomes (3-12 months post-surgery) and there is a clear need for long-term studies examining its safety.

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

Effectiveness

Thalamic stimulation compared to thalamotomy

A single high-quality randomised controlled trial of thalamic stimulation compared to thalamotomy in the treatment of different types of tremor was identified. This study provided some evidence that thalamic stimulation significantly improved some aspects of quality of life when compared to thalamotomy six months after surgery.

Pallidal stimulation compared to pallidotomy

A single randomised controlled trial reported that pallidal stimulation and pallidotomy were not significantly different at ameliorating drug-induced dyskinesias and some Parkinson's disease symptoms three months after surgery. However, this study was limited in its research methodology because of small sample size and lack of clarity in length of follow-up.

Sub-thalamic stimulation compared to ablative surgery

No studies were identified which statistically compared the effect of sub-thalamic stimulation with ablative surgery in Parkinson's disease patients.

In order to assume effectiveness of DBS (pallidal, thalamic and sub-thalamic) over ablative surgery, more rigorous study and reporting is required showing long-term and short-term effectiveness.

DBS compared to medical therapy

After reviewing the results of two health technology assessments (HTAs), it would appear some studies have demonstrated the added effect of DBS (thalamic, subthalamic and pallidal) over medical therapy. However, any conclusions regarding the effectiveness of DBS over medical therapy cannot be determined because of major methodological problems and poor quality of reporting in each of the studies used in the HTAs. More randomised controlled studies which look at long-term effectiveness and take full account of patients' quality of life are required in order to make a valid assessment of effectiveness.

Cost effectiveness

Cost effectiveness was based on one study which showed that thalamic DBS may improve some aspects of quality of life when compared to thalamotomy. The cost of DBS is estimated to be between $17,830 and $51,385 per patient more than current ablative techniques.

If daily function was maintained with DBS, which allows for further interventions to adjust electrodes and maximise potential functional activity gains, then there may be an advantage over ablative surgery. However, more studies demonstrating long-term effectiveness are required.

Recommendation

MSAC recommends that, based on the strength of evidence pertaining to deep brain stimulation for Parkinson's disease (MSAC Application No. 1031), interim public funding should be supported:

- for patients where their response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; and
- subject to the patients' participation in an appropriate controlled trial to obtain information on adverse events, longer-term patient outcomes and costs in the Australian setting. This should be carried out in consultation with appropriate groups and States, and should be limited to centres with necessary expertise.

This recommendation is to be reviewed no later than three years from the date of this report.

The Minister for Health and Aged Care accepted this recommendation on 19 June 2001.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of deep brain stimulation which is a therapeutic technique for the symptoms of Parkinson's disease. 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.

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 affairs and health administration.

This report summarises the assessment of current evidence for deep brain stimulation for the symptoms of Parkinson's disease.

Background

Deep brain stimulation for symptoms of Parkinson's disease

Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disorder that is characterised by the gradual death of selected but heterogeneous populations of neurons[1]. The pattern of cell loss is relatively specific for Parkinson's disease, involving the loss of dopaminergic cells in the substantia nigra of the midbrain. The substantia nigra influences the activity of the basal ganglia which are structures located near the base of the brain that are involved in movement regulation[2]. As these dopaminergic cells degenerate, the amount of dopamine produced is insufficient to maintain normal function.

Parkinson's disease symptoms and progression vary between patients but ultimately the disease leads to total disability in many people. Some of the major manifestations of Parkinson's disease include rigidity, tremor, bradykinesia and postural instability. Other concomitant symptoms such as dementia may also develop. Parkinson's disease patients are usually categorised by their symptoms. Tremor-dominant symptoms usually begin at a younger age with slower disease progression and a better continuation of cognitive functions, while patients with an older age of onset have predominantly postural instability and gait disturbances with more rapid disease progression and higher incidence of dementia.

Dopaminergic medication is used as a first line treatment for reducing the primary symptoms of Parkinson's disease. However, as the disorder progresses, medication can become less effective and has the potential to produce adverse effects such as dyskinesias and motor fluctuations. When patients become refractory to treatment they can spend their waking days fluctuating between on time (good motor function), on time with dyskinesias (good motor function disabled by dyskinesia) and off time (disabled by disease symptoms). Patients with symptoms inadequately controlled by medication may benefit from surgical treatment.

The Procedure

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

- thalamic stimulation is used predominantly for tremor;[3, 4]
- subthalamic stimulation for tremor, dyskinesia, rigidity, bradykinesia, akinesia, speech difficulties and freezing in the off state[3]; and
- pallidal stimulation for dyskinesias, reduction in off state (to increase overall mobility), tremor rigidity, bradykinesia and akinesia[3].

It is important to note however, that the exact target location and indication for each of these procedures is yet to be standardised[4].

In Australia, the most commonly used device for DBS is the Medtronic Model 3387 quadripolar lead (Medtronic, Inc., Minneapolis MN). The intracranial end of these leads have four platinum-iridium contacts 3mm apart and 1.5mm in length. The leads are connected to a battery-operated neurostimulator (Itrel II) which is implanted in the pectoral region of the body.

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. Initially patients need to be tested for their responsiveness to therapy. This is accomplished by implanting a lead at the relevant site using either stereotactic techniques such as image-guided stereotactic localisation or physiological techniques such as microelectrode mapping or macrostimulation. The implantation procedure is generally performed under local anaesthetic. Using a hand-held stimulator, the neurologist determines the patient's sensitivity and response to stimulation at a specific site. This procedure involves physical evaluation of the lower limbs and face muscles. Once the target that elicits the best response has been localised, the testing electrodes are removed and replaced with permanent leads.

Between 12 hours[5] and several days[6] after surgery to position the electrodes, the neurostimulator is implanted below the clavicle. During this procedure, patients are fully anaesthetised. Once the neurostimulator is internalised (a procedure using subcutaneous tunnelling), the neurologist adjusts the stimulation parameters (pulse width, stimulation amplitude and stimulation frequency) according to the patient's needs using an external programming unit. These stimulation parameters may vary but typically they have a pulse width of 60-120 μs, amplitude of 1-3 V and frequency of 135-185 Hz. After surgery the patient may turn the stimulator on or off with an external magnet according to the physician's instructions.

Intended purpose

For Parkinson's disease patients the key indication for 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. Pallidal stimulation is indicated in patients with severe tremor who do not respond to medication. Pallidal and thalamic and sub-thalamic stimulation are indicated for patients who have responded to treatment but whose reaction to medication has led to severe, unpredictable motor fluctuations and drug-induced dyskinesias. Before patients proceed to DBS, it is desirable for two neurologists to agree all drug manipulations have been exhausted.

There would appear to be a lack of evidence to indicate the proportion of Parkinson's disease patients refractory to drug therapy who may be considered for surgery. However, it has been suggested one to ten percent of patients with Parkinson's disease may be eligible[3]. In addition, the study by Nicholson & Milne[3] reported the majority of patients (approximately 67-75 percent) who present for pre-operative assessment are deemed by neurosurgeons to be unsuitable candidates.

Contraindications for DBS include dementia, extensive brain atrophy or systemic medical problems increasing 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 patients with concurrent infection.

Clinical need / burden of disease

This section describes Australian estimates of burden of disease, incidence, prevalence and mortality for Parkinson's disease. Burden of disease refers to the impact illness, injury, disability and premature mortality have on a 'healthy life'. The most common currency used to measure burden of disease is disability adjusted life years (DALY). The DALY scale measures the impact of both premature death and health problems among those who are living.

Nervous system disorders account for nine percent of the total disease burden, mostly in the form of disability[7]. Several of these disorders, such as dementia and Parkinson's disease, are highly age-associated, causing significant disability and sometimes death among older persons. Most patients with Parkinson's disease are over 50 years of age although at least ten percent of cases occur at an earlier age[7]. For women aged 65 years and older, nervous system and sense organ disorders contribute to 17.9 percent of the total burden of disease. Parkinson's disease contributes to 12.2 percent of this burden mainly through disability.[7] In men aged 65 years and older, the leading causes of disease and injury burden are cardiovascular disease and cancer. Parkinson's disease only makes a nominal contribution to the overall disease and injury burden. Health systems costs for Parkinson's disease for 1993-94 amounted to $149 million which was mainly associated with nursing home care[7]. The number of hospitalisations for Parkinson's disease in the 1997-98 fiscal year was 3,132 patients[7].

In 1996 the incidence of Parkinson's disease in Australia was estimated at 40 per 100,000 with a prevalence rate of 200 per 100,000 population[7]. Using Australian Bureau of

Statistics population figures for 1998,[8] it was estimated the prevalence for the population would be 37,200 cases and the annual incidence would be 7,480 cases. The age-standardised prevalence of Parkinson's disease is higher among females (260 per 100,000 compared to 130 per 100,000 for males), although mortality rates are higher in males (4 per 100,000 compared to 2 per 100,000 for females)[7]. Disease burden is also higher for females when compared to males. Disability adjusted life years for females was 14,312 compared to 11,264 for males. Years lost due to disability were also higher for females (12,210) compared to males (8,445)[9]. Table 1 lists Australian data for prevalence, mortality and disease burden (measured as disability adjusted life years and years of life lost due to disability) for Parkinson's disease. Data are age-standardised using the 1991 Australian population.

Table 1 Prevalence, mortality, disease burden and disease disability data*

	Prevalence (per 100,000)[a]	Mortality (per 100,000)[a]	Disease Burden (Disability Adjusted Life Years '000)[b]	Disability Burden (Years of Life Lost due to Disability '000)[b]
Male	130	4	11,264	8,445
Female	260	2	14,312	12,210
Total	390	6	25,576	20,655

a 1996 data taken from Australian Institute of Health & Welfare, Australia's Health 2000: the seventh biennial health report of the Australia Institute of Health and Welfare. 2000, AIHW: Canberra.

b 1996 data taken from Australian Institute of Health & Welfare, Mathers, C., Vos, T., et al., The burden of disease and injury in Australia. 1999, AIHW: Canberra.

Australian incidence and prevalence data for Parkinson's disease were calculated by using prevalence rates drawn from two European studies.[10, 11] These studies were combined to give a relative risk of mortality for Parkinson's sufferers of 2.7[12]. This figure was then applied to specific modelling software (DISMOD) to estimate incidence rates. The estimate of years lived with disability (YLD) used a mathematical model to account for progress through stages of the disease. This model was based on another European study, which calculated the distribution of severity levels in the population[13]. Underpinning these estimates of incidence and prevalence for Parkinson's disease in Australia is the assumption the European rates will apply to the Australian population. Since these studies showed no significant differences in Parkinson's disease prevalence across different European countries, it would be unlikely these rates would differ greatly in a developed country such as Australia.

The mortality counts were taken from deaths data compiled by the Australian Bureau of Statistics based on the State and Territory Registrars of Births, Deaths and Marriages. Age standardisation was used when comparing populations with different age compositions. The 1991 Australian population data from the ABS were used as the standard population for all intra-Australian comparisons, and the European and the World Standard Population statistics from WHO were used for international comparisons. The classification of deaths follows the Ninth Revision of the International Classification of Diseases. Diseases treated in hospitals and the procedures performed during a hospital stay are classified using the Australian version of the International Classification of Diseases, 9th Revision, Clinical Modification. These data recorded all deaths where the cause of death was code 332 (Parkinson's disease). Death certification is likely to understate Parkinson's disease as a contributing factor to mortality because sufferers often die of causes that are precipitated by the various associated incapacities.[14, 15] Hence these mortality data are likely to be an under-estimate of the true burden of this disease.

The National Hospital Morbidity Database includes data from public acute and (until 1997–98) Department of Veterans' Affairs hospitals, public psychiatric hospitals, private acute and psychiatric hospitals, and private free-standing day hospital facilities.

Exceptions within the public sector are public hospitals not within the jurisdiction of a State or Territory health authority or the Department of Veterans' Affairs (that is, hospitals operated by the Department of Defence, for example, and hospitals located in off-shore territories). In addition, data for a few small public hospitals in some jurisdictions (detailed below) were not available for certain years.

The one exception identified within the private sector is the only private hospital in the Northern Territory. In addition, data for a few small private hospitals in some other jurisdictions (detailed below) were not available for certain years.

In the private sector, separations were not available for private free-standing day hospital facilities in the Australian Capital Territory and the private hospital in the Northern Territory. About 19 percent of separations from Victorian private hospitals in general were not included.

Parkinson's disease has the greatest impact on those aged between 55 and 75 years[9]. Table 2 shows mortality, years of life lost due to mortality (YLL), years of life lost due to disability (YLD) and disability adjusted life years (DALYs), stratified by sex and age, for 1996. Mortality due to Parkinson's disease was highest for those aged over 55 years. Between 55 and 74 years of age, it would appear males have higher mortality rates and higher YLLs, YLDs and DALYs compared to females. As the population ages (i.e. 75+ years), the differences between males and females becomes less apparent for mortality rates and YLLs. However, for YLDs and DALYs it would appear females significantly surpass males beyond 75 years of age. This difference could be explained by females having overall lower mortality rates than men (i.e. they are more likely to be living to the age of 75+ than their male counterparts).

Table 2 Mortality, years of life lost due to mortality (YLL), years of life lost due to disability (YLD) and disability adjusted life years (DALYs) stratified by age and sex

	Total	Male	Female	Male					Female				
				0-14	15-34	35-54	55-74	75+	0-14	15-34	35-54	55-74	75+
Mortality	685	403	283	0	0	1	97	305	0	0	1	36	246
YLL	4921	2819	2102	0	0	19	1046	1754	0	0	21	460	1621
YLD	20655	8445	12210	0	0	0	5352	3094	0	0	0	4420	7790
DALY	25576	11264	14312	0	0	19	6397	4848	0	0	21	4880	9411

1996 data taken from Australian Institute of Health & Welfare, Mathers, C., Vos, T., et al, The burden of disease and injury in Australia. 1999, AIHW: Canberra.

Burden of disease data for Parkinson's disease is limited by case definition. Under-diagnosis or misdiagnosis is common for Parkinson's disease since the syndrome of parkinsonism may have a number of different causes such as drugs, Wilson's disease and other neurodegenerative diseases[1]. The current gold standard for the diagnosis of Parkinson's disease is neuropathological examination. At present there is no biological marker that unequivocally confirms this diagnosis[1]. It is also important to note mortality data for Parkinson's disease may be confounded by co-morbidities.

Existing procedures

Levodopa combined with adjunct medical therapy is the standard medical treatment for Parkinson's disease patients. However, prolonged use of levodopa can cause disabling motor fluctuations (variations in motor functions) and dyskinesias (abnormal involuntary movements). When medication is no longer effective or produces unacceptable side effects, surgical treatments may be a possible alternative.

The main surgical treatments for Parkinson's disease are ablative surgery and deep brain stimulation. Ablative surgery can include pallidotomy, thalamotomy and subthalamotomy. These procedures involve destroying specific parts of the brain such as the globus pallidus, thalamic and subthalamic nucleus. A variety of sites can also be used within these targets (e.g. posterolateral or posteroventral, areas of the GPi and 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. As described in the previous section, deep brain stimulation involves the stimulation of specific targets (i.e. the same tissue targeted in ablative surgery) using electrodes connected to an implanted stimulator. Although both ablation and stimulation have hitherto concentrated on the STN and GPi, it would appear the subthalamic nucleus is becoming the preferred target[3].

Comparator

In order to assess the effectiveness of DBS against existing surgical procedures, ablative surgeries such as pallidotomy, thalamotomy or subthalamotomy were selected as the appropriate comparators. In order to assess the effectiveness of DBS in itself, other comparators such as standard medical therapy in the form of medication or placebo (i.e. stimulation turned ON compared to stimulation turned OFF) were also considered.

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 implantable devices and non-implantable devices (see Table 3).

Table 3 TGA Listing and Registration numbers

Implantable devices	TGA Registration or Listing numbers
Model 3387DBS™ Lead	AUST R 56143
Model 7495 Extension	AUST R 56143
Model 7424 Itrel® Neurostimulator	AUST R 56143
Burrhole ring and Cap	AUST L 33287
Non implantable medical devices used in conjunction with the procedure	
Model 7432 Console Programmer	Exempt
Model 7458 MemoryMod® Software Cartridge	Exempt
Model 7458 Patient Magnet	Exempt
Model 3625 Test Stimulator	AUST L 63348
Model 3353/3354 Lead Frame Kit plus accessories	AUST L 33287

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 arrangements

It is believed deep brain stimulation is currently billed under a combination of Medicare Benefits Schedule items. These include Item 40801 (functional stereotactic procedure including computer assisted anatomical localisation, physiological localisation and lesion production in the basal ganglia, brain stem or deep white matter tracts) and Item 39134 (subcutaneous placement of spinal neurostimulator receiver or pulse generator).

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period between January 1966 and September 2000. Searches were conducted using the databases listed in Table 4.

Table 4 Electronic databases including versions used in the review of clinical effectiveness of DBS

Databases	Version and database updates
Cochrane Library including:	CD - ROM Issue 3, 2000
the Cochrane Databases of Systematic Reviews	
the Database of Abstracts of Reviews of Effectiveness	
the Cochrane Controlled Trials Register	
Medline (Ovid and PubMed)	1966 to October Week 4 2000[a]
PsycINFO (Ovid)	1967 to September Week 1 2000
CINAHL (Ovid)	1982 to August 2000
Current Contents (Ovid)	1993 Week 26 to 2000 Week 38
PreMedline (Ovid)	September 15 2000
HealthStar	1975 to September 2000
Trip	September 14 2000
Australasian Medical Index (SilverPlatter)	September 14 2000

a Currency of Medline at time of searching

The search strategy outlined in Table 5 was employed to retrieve articles that compared the clinical effectiveness of deep brain stimulation to ablative surgery or medical treatment, and articles that incorporated safety issues associated with the use of deep brain stimulation.

Table 5 Search terms used to identify citations for clinical effectiveness of DBS

Text words and Mesh terms
Parkinson's disease[c], Parkinson[a,b] Globus Pallidus[c], Pallid [a,b]
exp Thalamus [c], Thalam [a,b]
exp Subthalamus [c], Subthalam [a,b]
Entopeduncular nucleus.tw
Electric stimulation therapy [c], Electric stimulation [c], Electric [a,b] adj stimul [a,b]
Electrodes implanted[c], Implant[a,b] adj electrode[a,b]
Brain stimul [a,b], Neurostimul [a,b], Thalam[a,b], adj stimul[a,b], Chronic stimul [a,b]
exp Stereotaxic techniques [c]
Stereota [a,b]
Ablat [a,b]

a Represents Wild card
b Terms were searched as text words
c Terms searched as MeSH headings
exp Explodes terms to include narrower terminology

Health technology assessments

Four health technology assessments (HTAs) were identified that purported to investigate the effectiveness of deep brain stimulation.[3, 16-18] Selection or exclusion of these HTA reports was based on the inclusion and exclusion criteria described on the next page. A final decision to reject or accept the selected HTAs was based on a thorough reading of the complete report. Electronic searching included accessing the Internet sites of the following health technology assessment groups:

Agencia de Evaluación de Tecnologias Sanitarias (AETS)

Agencia de Evaluación de Tecnologías Sanitarias de Andalucia (AETSA)

Alberta Heritage Foundation for Medical Research (AHFMR)

Agency for Healthcare Research and Quality (AHRQ)

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

L'Agence Nationale pour le Developpement de l'Evaluation Medicale (ANDEM)

British Columbia Office of Health Technology Assessment (BCOHTA)

Catalan Agency for Health Technology Assessment

Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

Center for Medical Technology Assessment (CMT)

College voor Zorgverzekeringen (CVZ)

Conseil d'évaluation des technologies de la santé du Québec (CETS)

German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DAHTA@DIMDI)

Danish Institute for Health Technology Assessment

Danish Institute for Health Services Research (DSI)

ECRI

Unidad De Tecnologias De Salud (ETESA)

EUROSCAN

Finnish Office for Health Care Technology Assessment (FinOHTA)

Health Council of the Netherlands (GR).

Minnesota Health Technology Advisory Committee (HTAC)

Instituto Nacional de Higiene Epidemiologia y Microbiologia (INHEM)

Institute of Technology Assessment of the Austrian Academy of Science (ITA)

International Network of Agencies for Health Technology Assessment (INAHTA)

International Society of Technology Assessment in Health Care (ISTAHC)

Australian Safety and Efficacy Register of New Interventional Procedures- Surgical (ASERNIPS)

Medical Technology & Practice Patterns Institute (MTPPI)

National Coordinating Centre for Health Technology Assessment (NCCHTA)

New Zealand Health Technology Assessment (NZHTA)

National Institute for Clinical Excellence (NICE)

National Horizon Scanning Center (NHSC)

Netherlands Organization for Scientific Research (NWO)

Basque Office for Health Technology Assessment (OSTEBA)

Swedish Council on Technology Assessment in Health Care (SBU)

The Norwegian Centre for Health Technology Assessment (SMM)

Swiss Science Council/Technology Assessment (SWISS/TA)

TNO Prevention and Health (TNO)

Veterans Affairs Technology Assessment Program (VATAP)

WHO Health Technology Assessment Programme (Collaborating Centres)

Inclusion and exclusion criteria

Identified citations were filtered through a multilevel review process. Article selection and exclusion were based on the criteria outlined below.

Population

Inclusion: Patients with severe Parkinson's disease where medication is no longer effective or produces severe side effects. The results of studies which used mixed populations of patients i.e. Parkinson's disease and essential tremor were included if they separately and adequately reported data for patients with Parkinson's disease.

Exclusion: Parkinson's disease not refractory to drug treatment.

Intervention

Inclusion: Deep Brain Stimulation: Pallidal, Thalamic, Sub-thalamic.

Exclusion: Combined DBS and contralateral thalamotomy or pallidotomy.

Comparators

Inclusion: Control treatments including ablative procedures such as pallidotomy and thalamotomy, or medical treatment such as on or off medication, or stimulation turned OFF.

Exclusion: Studies not using the comparators outlined above.

Outcomes

Inclusion: Parkinson's disease symptoms assessed by Unified Parkinson's disease Rating Scales, Hoehn & Yahr scale, duration of response (*e.g.* time when there is absence of shaking). Patient-based outcomes such as quality of life, drug usage and adverse effects.

Exclusion: Physiological outcomes alone.

Methodology

Inclusion: Comparative studies published as original articles and systematic reviews of studies that compare the outcomes of patients who undergo DBS with a group of patients who have been assigned to a control treatment such as ablative procedures (pallidotomy, thalamotomy or subthalamotomy), or medical treatment (such as on or off medication, or stimulation turned OFF).

Exclusion: Case reports, case series and non-systematic reviews of DBS, opinions published as editorials or letters to the editor, descriptive studies, consensus-based evidence.

Data Extraction

An initial assessment of the abstracts allowed for the exclusion of articles that did not meet the selection criteria. Ambiguous or unclear citations proceeded to the next stage. Two independent reviewers examined each citation for inclusion. Discrepancies in selection were discussed and resolved through consensus. The search to retrieve articles that compared the clinical effectiveness of DBS with ablative surgery or medical treatment yielded 692 articles, of which 662 were rejected (70 percent evaluated DBS as a single intervention, 18 percent evaluated DBS with adjunctive ablative surgery, 8 percent did not provide comparative data, and the remainder were narrative reviews). Thirty articles were finally assessed in full text form. All were English language articles. Of these 30 articles, twelve compared DBS with ablative surgery and 17 compared DBS with medication (on or off) with stimulation turned OFF.

With respect to articles comparing DBS with ablative surgery, two were randomised-controlled trials, six were non-randomised comparative studies and four were unclear. For DBS compared to medical treatment or stimulation turned off, three health technology assessments were retrieved along with 15 additional articles published since the release of the latest health technology assessment. Full text articles of these citations were retrieved and assessed. A final decision to reject or accept articles was based on a thorough reading of the complete article. Only the studies that successfully passed this process were included in the report.

Assessment of quality

All accepted articles underwent assessment of study quality based on criteria that focus on important aspects of study design (Table 6).[19, 20]

Table 6 Domains and levels used in the assessment of methodologic quality

Randomisation	
Adequate	Adequate measures to conceal allocations such as central randomisation; serially numbered, opaque, sealed envelopes; or other descriptions that contain convincing elements of concealment
Unclear	Inadequately concealed trials in which the author failed to describe the method of concealment with enough detail to determine its validity
Inadequate	Method of allocation is not concealed, such as alternation methods or the use of case numbers
None	No randomisation method was employed
Masking	Masking strategy applied (triple, double, etc.)
Losses to Follow-up	Losses specified.

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence, which is shown in Table 7.

Table 7 Designation of levels of evidence

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 pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and 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 and post-test.

Source: NHMRC National Health and Medical Research Council, A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: NHMRC, 1999.

Expert advice

A supporting committee with expertise in Parkinson's disease management was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Is it safe?

To investigate the incidence and types of adverse effects associated with DBS for Parkinson's disease, the literature was searched to obtain the full-text version of all records which appeared to be original reports and either:

- mentioned adverse effects or events in the abstract;

  OR

- from the title or abstract, looked as though they would address adverse effects or events.

This is by no means a comprehensive approach. However, it is believed these articles will be representative of the majority of studies.

Some of the studies included patients who may not have been refractory to drug treatment. Several reports included patients with Parkinson's disease and essential tremor, and the adverse effects or events were often not distinguished by patient type. Generally, adverse effects (other than cognitive) were stated to be mild and reversible, often improving when the level of stimulation was reduced. The tables below (Tables 8-11) present the adverse effects and events associated with DBS according to the target area of deep brain stimulation.

The number of articles addressing stimulation of either the ventral intermediate thalamic nucleus (VIM), sub-thalamic nucleus (STN) or globus pallidus internus (GPi) were similar (16, 16 and 17 respectively) but the number of patients within studies varied. As numbers of patients experiencing particular effects have often not been supplied, this list of adverse events is indicative but not quantitative.

The adverse effects reported were both long- and short-term. However, the long-term safety of DBS is yet to be established, with the majority of studies following patients between three and twelve months.

The approval of the DBS device by the United States Food and Drug Administration was subject to Medtronic conducting further studies examining the long-term safety and effectiveness of the procedure. Of particular concern was the time required to replace lead wires and the effect of long-term stimulation on brain tissue[21].

Table 8 Adverse effects and events associated with stimulation of the Subthalamic Nucleus (STN)

	Associated with surgical procedure:	Functional:	Cognitive or behavioural:
Subthalamic Nucleus (STN)	Haematoma[22-24] Difficulty with placement of extension wire[25] Infraclavicular haematoma[25] Subcutaneous infection at site of extension lead[23, 26] Removal and reimplantation of extension lead[26] Replacement of lead and generator[23] Grand mal seizure after ventriculography[27] Eyelid apraxia (induced or increased by surgery[23] Weight gain[23, 26, 28] Unilateral anisocoria[28] Frontal area contusion along electrode tract[24]	Hemiballism[22, 28] Dyskinesia[23, 25, 27-29] Dystonia[25] Transient paraesthesia[25, 28] Disequilibrium[23, 25] Dysarthria[25] Dysphagia[25] Hypomimia[25] Hypophonia[23, 25, 28] Persistent severe paralysis and aphasia (due to haematoma)[23]	Reduction in fluency[30, 31] Depression[28, 32] Transient euphoric state with laughter[32] Confusion and disorientation[22-24, 27] Anxiety during removal of frame[25] Transient delirium[25] Bradyphrenia[27] Lack of energy and initiative, abulia[27, 28, 33] Involuntary intermittent laughter[34] Hallucinations[23] Temporo spatial disorientation[23] Decrease in verbal fluency[24, 28]

Table 9 Adverse effects and events associated with stimulation of the Thalamus (site not specified)

	Associated with surgical procedure:	Functional:	Cognitive or behavioural:
Thalamic (further detail not provided.)	Pain, swelling at site of stimulator[35] Difficult to anchor antenna[35] Transient scalp excoriation without loss of electrode[35]	Parkinsonian crisis[35] Dysarthria[35] Ataxia[35] Gait disturbance[35] Paraesthesia[35] Transient nausea, faintness[35] Escalation of stimulator voltage[35]	Transient emotional lability, confusion[35]

Table 10 Adverse effects and events associated with stimulation of the Ventral Intermediate Thalamic Nucleus

	Associated with surgical procedure	Functional	Cognitive or behavioural
Ventral Intermediate Thalamic Nucleus (VIM)	Haematoma[6, 33, 36-38] Microhaematoma[22, 29, 39, 40] Haemorrhage[36-38, 41] Skin erosion or infection[6, 29, 33, 36, 38-40, 42] Transient fluid collection in subclavicular pocket of stimulator[39] Electrode breakage, dislocation or withdrawal[36, 42] Lead displacement or breakage[36-38] Removal and reimplantation of extension cable[40] Removal of lead[29] Catheter disconnections[36] Replacement of electrode path during surgery[43] Replacement of electrode[33] Replacement of neuropacemaker, generator[6, 44] Reoperation[29] Local pain at site of generator[33] Mild shock in infraclavicular area when generator turned on[45] Death related to surgery[6]	Transient paraesthesia[6, 22, 29, 36, 37, 39, 40, 44, 46, 47] Permanent paraesthesia[38] Dysarthria[6, 22, 29, 36-40, 42, 45, 46, 48] Dystonia[6, 22, 29, 33, 38-40, 46, 48] Rebound tremor[22, 29, 36, 43, 44] Persistent disabling tremor necessitating thalamotomy[43] Disequilibrium[6, 22, 29, 33, 36, 37, 39, 40, 42, 45-47] Tonic posture of fingers during stimulation[43] Lateropulsion[48] Headache[36, 47] Nausea[36, 47] Weakness[36] Burning sensation in perioral and ophthalmic region[39] Transient ideo-motor slowing[44] Ataxia[6, 42] Loss of tremor control with implantation of contralateral lead[45] Impaired eye movement[6] Facial paresis[6] Hypesthesia[6]	Mild confusion and disorientation[22] Transient attentional and cognitive deficit[33] Decrease in fluency, especially verbal[39, 49] Decrease in spatial performance[39] Subtle cognitive defects[46] Mild short-term memory loss[45] Transient altered mental status[47] Diplopia[47]

Table 11 Adverse effects and events associated with stimulation of the Globus Pallidus internus (GPi)

	Associated with surgical procedure	Functional	Cognitive or behavioural
Globus Pallidus internus (GPi)	Infection over distal portion of pulse generator[50] Haemorrhage[24, 49, 51] Surgical repositioning of lead[49, 51] Frontal contusion along electrode tract[24] Rejection reaction and secondary infection[52] Removal and replacement of system[52] Lead dislodgement[53] Skin erosions and infections[53] Removal of generator[53] Neuralgia associated with small granuloma at site of connector[53] Surgical revision[53] Aseptic hyperthermia[54]	Transient visual flash[55] Optic sensations[53] Dyskinesia[27, 50, 55] Akinesia[55] Worsening of gait[55] Crural paresis[5] Transient paraesthesia[25] Paraesthesia[51, 54] Disequilibrium[25] Dysphagia[25] Hypomimia[25] Hemidystonia[50] Dystonia[27, 50, 51, 53] Transient phosphenes[50] Intermittent gait failure[50] Temporary increase in freezing episodes[53] Hypophonia[27] Freezing[27] Hemiparesis[51] Mild hand tremor[27] Posturing of hand[27] Ataxia of eyelid[27] Tolerated much smaller reduction in dopaminergic medication than STN patients[41] Choreiform movements of foot[51] Choreoathetosis of leg[53] Nausea[54] Thoracic oppression[54] Seroma[5]	Confusion and disorientation[22, 24, 27, 53] Executive function dramatically impaired with stimulation on[56] General malaise[60] Significant deterioration of performance on Visual Conditional Associative Learning test[57] Loss of sleep benefit[27] Bouts of mania and hypomania[58] Transient speech difficulty[51] Visual disturbances[51] Longer latency in simple choice reaction time[24] Increased number of errors in spatial working memory[24] Increase in Mattis Dementia score[24] Decrease in semantic verbal fluency[49] Decline in general cognitive performance[59] Significant reduction in subscale for language CAMCOG tests[53] Severe depression[54] Psychosis and hallucinations[5]

Is it effective?

Deep brain stimulation versus ablative surgery

Twelve articles were identified which purported to compare the effects of DBS with ablative techniques. A full review of these studies identified four that statistically compared patients receiving DBS with those receiving either thalamotomy or pallidotomy. No evidence comparing sub-thalamic stimulation with ablative surgery was found. Of the studies selected for inclusion, two were randomised controlled trials (Schuurman, Bosch et[6] and Merello[60]) and two were retrospective cohort studies (Tasker, Munz et al[61] and Tasker[35]). The study by Tasker[35] is essentially an update of the earlier study by Tasker, Munz et al, with the addition of some outcome variables.

Published randomised controlled trials comparing DBS with ablative procedures

Table 12 outlines the characteristics of the randomised controlled trials included in this review. The paper by Schuurman, Bosch et al[6] is a randomised-controlled trial (RCT) of 45 patients with severe Parkinson's disease. While this trial also included patients with essential tremor and multiple sclerosis patients, results from these patients will not be discussed. Of the Parkinson's disease patients, 22 were randomised to thalamic DBS and 23 were randomised to thalamotomy.

The second study by Merello[60] is also a randomised controlled trial. However this study compared pallidal DBS with pallidotomy. This study was relatively small in comparison to the Schuurman study, having a sample size of only 13, six of which were randomised to pallidal stimulation and seven to pallidotomy. Pre- versus post-surgery assessments for Parkinson's disease symptoms, capacity to carry out daily living activities and adverse effects were compared between the two surgical groups.

Table 12 Descriptive characteristics of RCTs comparing DBS with ablative surgery*

First Author Year of Publication & Location	NHMRC Level of Evidence	Study Design	Dates of Enrolment	Characteristics of Study Population		
				Size	Age (in years)	Sex Ratio (M:F)
Schuurman et al (2000)[6] Netherlands	II	RCT	June 1995 to Oct 1998	T-DBS=22 T=23	T-DBS=63±8.9[b] T=68±7.9[b]	Not stated
Merello (1999)[60] Argentina	II	RCT	Not stated	P-DBS=6 P=7	P-DBS=59.1±6.4[b] P=55.3±9.8[b]	P-DBS=4:2 P=5:2

* Abbreviations: T-DBS = Thalamic DBS group; P-DBS = Pallidal DBS group; T = Thalamotomy group; P = Pallidotomy group; M = male; F = female

[b] Mean ± standard deviation

Study quality

The study by Schuurman, Bosch et al[6] was of higher methodological quality than the Merello[60] study.

Method of randomisation was described only in the Schuurman, Bosch et al study which used a computer-generated code with adjustment for the cause and extent of tremor (unilateral versus bilateral) to assign surgical treatment. The study by Merello merely stated that the study was randomised. Both papers provided inadequate information regarding the randomisation process, thus making it difficult to ascertain whether there was sufficient concealment of allocation.

Losses to follow-up were reported by Schuurman, Bosch et al[6] using intention-to-treat analysis to account for them. Losses to follow-up were not reported in the study by Merello[60] which may bias the results if those withdrawing from the study were different in terms of adverse outcomes than those included in the final analysis. In addition, the length of follow-up in both of these studies was relatively short. The follow-up period in the Merello study was a maximum of just three months while follow-up in the Schuurman, Bosch et al study did not go beyond six months. In fact, one of the major methodological limitations with the Merello paper was the confusion regarding the length of follow-up of some patients (i.e. whether the results related to 24 hours or 1-3 months post surgery).

Another major limitation of Merello's paper was study power. This study had a total of 13 patients (six in the DBS group and seven undergoing pallidotomy) which may not have been sufficient to detect a significant difference between the treatment groups. The study by Schuurman, Bosch et al[6] reported that 32 patients would be needed in each treatment arm to detect a five point difference in the Frenchay Activities Index at 80 percent power and 0.05 significance level. Blinded assessment was performed for some outcome measures in both studies. Schuurman, Bosch et al[6] performed single blinded evaluations for tremor. All other outcomes were assessed open label. In the Merello study[60], neuropsychological outcomes were assessed single blinded while the remaining motor examinations were performed open label. Table 13 outlines the methodological quality of these studies.

Table 13 Methodological quality of included studies comparing DBS with ablative surgery

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Schuurman et al (2000)[6]	RCT	Unclear	Single blinded for tremor	Total Losses n=4 n=2 Parkinson's disease patients from the DBS group. n=2 group unknown
Merello (1999)[60]	RCT	Adequate	Single blinded for neuropsychological outcomes	Unclear

Abbreviations: RCT = randomised controlled trial ;T-DBS = Thalamic DBS group; P-DBS = Pallidal DBS group; T = Thalamotomy group; P = Pallidotomy

Patient Criteria

Schuurman, Bosch et al[6] recruited 45 Parkinson's disease patients referred by neurologists throughout the Netherlands for consideration as candidates for randomisation to surgery. Thirteen patients were recruited by Merello[60]. Schuurman et al assessed patients using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn Yahr scale. Patients were included in this study if they had severe bilateral or unilateral tremor for at least one year as defined by these two instruments. Patients in the Merello[60] study were included if they met the Core Assessment Program for Intracerebral Transplantations – Posteroventral Pallidotomy (CAPIT-PVP) program criteria. Since these studies used different inclusion criteria, they may in fact have different study populations i.e. Parkinson's disease patients with different disease severity. Table 14 provides the patient inclusion and exclusion criteria for each of the reviewed studies.

Table 14 Patient criteria of included studies comparing DBS with ablative surgery

First Author and Year of Publication	Patient Criteria
Schuurman et al (2000)[6]	Inclusion: Patients with severe unilateral and bilateral tremor for at least one year as defined by Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn Yahr scale; Exclusion: Less than 18 yrs of age; cognitive dysfunction of <24 on the mini mental state exam; contraindications for surgery (unstable cardiac or pulmonary disease or coagulation disorders); advanced cerebral atrophy on CT scan; previously undergone thalamotomy
Merello (1999)[60]	Inclusion: Patients with idiopathic Parkinson's disease who met the Core Assessment Program for Intracerebral Transplantations (CAPIT)-PVP program criteria; The CAPIT-PVP consists of patients with 1) bradykinesia and rigidity as cardinal features; 2) severe peak of dose or biphasic dyskinesias; 3) marked asymmetry of signs; 4) absence of significant changes in ADL score during drug period on and drug period off examinations (as a result of dyskinesias); 5) absence of dementia. Exclusion: Poor surgical candidates because of unstable medical condition, dementia, major depression or psychosis

Interventions examined

The two studies described in detail the treatment regimens to which patients were exposed. Both unilateral and bilateral procedures were conducted depending on the need of the patient. In the study by Schuurman, Bosch et al[6] both comparison and intervention targeted the VIM thalamic nucleus which was identified by ventriculography according to the stereotactic atlas. Macroelectrodes were applied intraoperatively to identify optimal site for lesion or electrode. Site selection was dependent on 1) lowest threshold high-frequency stimulation being maximal at 130Hz and 2) no side effects presenting at high (130Hz) and low frequency (2Hz). For thalamic stimulation a four-contact electrode was implanted (model 3387DBS, Medtronic, Minneapolis) with the second distal contact on the target site. After several days of testing, electrodes were connected to an implantable pulse generator (Itrell II, Medtronic). In the thalamotomy group, a lesion was produced using the bare tip of a 1.5 by 3.8mm macroelectrode at a temperature of 40°C for 60 seconds.

Merello[60] targeted the basal ganglia in both patient groups. Activity at this site was recorded using platinum/iridium microelectrode. The number of recordings was dependent on:

- the ability to identify GPe and GPi;
- the presence of a motor drive;
- identification of internal capsule by microstimulation; and
- correct identification of the optic tract by microstimulation and activity-recording after visual stimulation.

After carrying out all these steps, GPi macrostimulation at 50, 150 and 300Hz was performed and clinical results were evaluated by tapping score and UPDRS items. The pallidal stimulation group was implanted using a 3387 Medtronic lead connected to an Itrel II Medtronic multiprogrammable pulse generator, which was turned on 12 hours post surgery. Stimulator parameters were based on those providing best relief of symptoms. The pallidotomy group underwent lesioning of the globus pallidus at 75°C for 60 seconds using an electrode of 2mm diameter and 4mm length.

Variations in surgical procedures for DBS and ablative surgery have been identified in the literature[3]. Even within broad intervention categories there is variation in the location and size of the target sites. This variation may directly influence the efficacy of the intervention.

Study Results

Thalamic stimulation versus thalamotomy

The study by Schuurman, Bosch et al[6] compared patients undergoing thalamic stimulation (n=22) with those undergoing thalamotomy (n=23). This study assessed patients at baseline and postoperatively at six months. The primary outcome measure was change from baseline in functional status as measured by the Frenchay Activities Index. This index assesses 15 activities of daily living involving domestic tasks (i.e. preparing meals, washing up, washing clothes or doing heavy and light housework). An increase of five points was associated with a clinically relevant outcome. Secondary outcome measures were tremor of the arm, adverse effects, and patients' opinions regarding their surgical outcomes.

Frenchay Activities Index: At six months follow-up, patients receiving thalamic stimulation scored significantly better than those receiving thalamotomy even after adjusting for base-line characteristics such as age, gender, cause of tremor, severity of disease and baseline. The Frenchay scores were as follows: DBS group 5.5±6.3 versus Thalamotomy 0.8±4.9; the difference between the groups was 4.7, 95 percent CI 1.2–8.0.

Tremor: At six months follow-up there was no significant difference between the two groups in relation to severity of tremor. In fact greater than 85 percent of patients in both the thalamic stimulation and the thalamotomy groups had complete suppression of tremor (i.e. tremor score of 0).

Patients' opinions of functional status: This was not exclusively reported for Parkinson's disease patients. Results presented in the article were pooled for Parkinson's disease and essential tremor patients.

Adverse effects: Complications from surgery at six months would appear to be more frequent for thalamotomy than thalamic stimulation although their rate of occurrence was too small to warrant statistical analysis. It is important to note, however, that one patient receiving thalamic stimulation died as a result of surgery whereas no mortality was observed for any patients in the thalamotomy group.

Published lower levels of evidence comparing thalamic stimulation with thalamotomy

Two retrospective cohort studies were identified which compared thalamic DBS with thalamotomy (Tasker[35] and Tasker, Munz et al[61]). However, these studies suffer from serious methodological limitations and their results will only be discussed briefly. Since nearly all of the results from these studies have been pooled for essential tremor and Parkinson's disease patients, only those outcomes that have been presented separately for Parkinson's disease patients will be given. Tasker, Munz et al[61] reported that the effects of DBS and ablative surgery on rigidity and Parkinsonian writing were similar.

However DBS was more effective in improving manual dexterity in Parkinson's disease patients than thalamotomy. Whether these results were statistically significant is uncertain since no analysis was undertaken. In addition, it was difficult to interpret the number of patients on which these results were based since the total number for each intervention was not presented and the percentages in the tables did not add up to 100 percent. The Tasker[35] study reported no significant differences in rigidity between the thalamic stimulation and thalamotomy groups (32.9 percent reporting the same or worse rigidity in the DBS group compared to 31.4 percent in the thalamotomy group; $?^2=0.90$, df=2, p=0.637; these results were extrapolated from the data presented in the paper). No other results were presented separately for Parkinson's disease.

These results should be interpreted with caution in light of significant methodological limitations which include the differences in follow-up within and between the thalamic stimulation and the thalamotomy groups. Postoperative follow-up for patients varied from three to six months to more than five years. In addition 95 percent of thalamic stimulation patients were followed up for a period of less than two years, whereas 50 percent of patients in the thalamotomy group were followed up for a period of two years to more than five years. This poses major problems in interpreting the results. These studies also included patients having received previous ablative surgery in addition to thalamic stimulation in the DBS group. Patients such as these needing additional surgery fit into a specialised group requiring separate analysis.

Pallidal stimulation versus Pallidotomy

The study by Merello[60] compared patients undergoing posteroventral stimulation (PVS) (n=6) with those undergoing posteroventral pallidotomy (PVP) (n=7). This study purported to assess patients at baseline and postoperatively at three months.

The primary outcome measures were the Unified Parkinson's Disease Rating Scale (UPDRS version 3.0 rating from 0–56) and the Activities of Daily Living (ADL) in the drug on and off states. Secondary measurements were performed using UPDRS sub-items for ADL - bradykinesia, tremor, rigidity, gait and postural instability as well as a timed arm test (time to tap index finger between two points 30cm apart for 20 successive cycles). Dyskinesia was only evaluated for the drug on state. In addition a composite score was developed for postural instability and gait disorders (PIGDS) by adding the individual scores for these items. Neuropsychological and neuropsychiatric tests were also assessed at baseline and two to three days after surgery. These included:

- Raven's Progressive Matrices (Wisconsin Card Sort Test - WCST) to measure the ability to develop new concepts;
- Controlled Oral Word Association Test to examine access to semantic information with time constraint;
- Buschke Selective Reminding Test to measure verbal learning, recall and recognition;
- Benton Visual Retention Test to assess visual perception and non-verbal memory;
- Digit Span to examine auditory perception;
- Perdue Pegboard to assess manipulative dexterity;
- Hooper Visual Organisation Test to assess visual organisation;
- Benton Visual Form Discrimination to assess visual discrimination; and
- Block Design (Wechsler adult intelligence scale - WAIS) to establish the presence of constructional ataxia.

All outcomes except dyskinesias were assessed in the drug off state.

UPDRS scores: No significant differences in improvement for UPDRS motor scores were observed between pallidal stimulation and pallidotomy for both the drug on (percentage of improvement PVP 29.7 versus PVS 28.7, NS (not significant)) and off state (percentage improvement PVP 3.8 versus PVS 7.5, NS).

ADL: No significant differences between PVP and PVS were observed (data not provided)

Hand Tapping Score: Post-surgery stage tapping scores in the drug off state were significantly improved in the PVS group compared to those receiving PVP for the non-operated side (29.7±16 versus 25.1±10.1, $p<0.05$). No significant differences were observed between the groups post-surgery for the operated side. More importantly the magnitude of change from pre- to post-surgery was not significantly different between the groups for both the non-operated and operated sides.

Dyskinesias: Post surgery dyskinesia was observed to be significantly worse in the PVS group for the head, trunk and operated upper limb compared to the PVP group (Head: PVP 0.44±0.9 versus PVS 1.25±1.1, $p<0.05$; Trunk: PVP 0.31±0.8 versus PVS 1.25±0.75, $p<0.05$; Operated upper limb: PVP 0.13±0.3 versus PVS 1.8±0.6, $p<0.05$). It is important to note, however, that the dyskinesia scores were extremely low for both groups. In addition, the percentage improvement from pre- to post-surgery was not significantly different between the PVP and PVS groups for any areas of the body that were tested.

Rigidity: No significant differences between PVP and PVS were observed for improvement in rigidity from pre- to post-surgery for either the contralateral (PVP 42.8 percent versus PVS 22.7 percent, NS) or ipsilateral side (PVP 77.6 percent versus PVS 72 percent, NS).

Tremor: No significant differences between PVP and PVS were observed for improvement in tremor from pre- to post-surgery for either the contralateral (PVP 27 percent versus PVS 0 percent, NS) or ipsilateral side (PVP 44 percent versus PVS 46 percent, NS).

Bradykinesia: No significant interactions or differences in groups (PVP versus PVS) or time (pre- to post-surgery) were observed.

PIGD: No significant improvement in PIGD was observed post surgery for PVP or PVS for either drug on or off. Percentage change from pre- to post-surgery was also not significant between groups (Drug off PVP 37.2 percent versus PVS 20 percent, NS; Drug on: PVP zero percent versus PVS 20 percent, NS).

Neuropsychological findings: A three-way repeated analysis of variance measure - ANOVA (group (PVP or PVS) x task (neuropsych test) x time (pre- to post-test)) showed no significant group by time interaction ($F[1,2]=0.39$, NS) or significant group by time by task interaction ($F[11,22] = 0.75$, NS).

Adverse effects: In total, six out of thirteen patients presented with transient complications after surgery. In the PVP group, two patients had difficulty swallowing which led to aspirate pneumonia and another patient had subdural haematoma that spontaneously reabsorbed within two weeks. In the PVS group, one patient had mild crural paresis that resolved within the first month, one patient had psychosis and hallucinations and one patient had a seroma.

Sub-thalamic stimulation compared to ablative surgery

No studies were identified which statistically compared the effect of sub-thalamic stimulation with ablative surgery in Parkinson's disease patients.

Summary of effectiveness of DBS versus ablative surgery

There is some evidence that thalamic stimulation significantly improves some aspects of quality of life when compared to thalamotomy six months after surgery. One study reported that pallidal stimulation and pallidotomy were not significantly different in ameliorating Parkinson's disease symptoms three months after surgery. No studies were identified which compared subthalamic stimulation with ablative surgery. Evidence of effectiveness of DBS (pallidal, thalamic and sub-thalamic) over ablative surgery therefore still requires more rigorous study and reporting. More randomised controlled studies which look at long-term effectiveness and take full account of patients' quality of life in addition to Parkinson's disease symptoms are still required in order to make a valid assessment of effectiveness.

Deep brain stimulation versus medical treatment

Due to the paucity of high level evidence comparing DBS with ablative surgery, a decision was made to compare the effect of DBS with medical treatment instead. This review assessed the effectiveness of deep brain stimulation based on critical appraisal of health technology assessments and randomised controlled trials examining this procedure.

Critical appraisal of published Health Technology Assessments

This review identified three Health Technology Assessments that summarise the literature on DBS.

- Nicholson T and Milne R, *Pallidotomy, thalamotomy and deep brain stimulation for severe Parkinson's disease*. 1999, Wessex Institute for Health Research and Development, Development and Evaluation Committee (DEC): Southampton[3].

- ECRI, *Thalamic stimulation for Parkinson's disease*. 1999, ECRI Health Technology Assessment Information Service: Plymouth Meeting[17].

- Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA), *Evaluación de los tratamientos quirúrgicos de la enfermedad de Parkinson.* 1999, Junta de Andalucía: Seville[18].

Of the three Health Technology Assessments, only the results of the DEC report will be discussed. The findings of the AETSA report were based exclusively on low level evidence and the results of the ECRI report were not freely available.

DEC Report

The DEC report aimed to review the effectiveness of pallidotomy, thalamotomy and deep brain stimulation for severe Parkinson's disease. This review only considered English language articles incorporating the words 'randomisation', 'blinded assessment' or 'trial' in the title or abstract. The results of this health technology assessment were based on five crossover randomised studies, which used blinded assessment of outcomes with the stimulator ON or OFF. Conclusions regarding the effectiveness of DBS have not been reported in this review because of the major methodological problems and poor quality of reporting in each of the studies.

Methodological limitations of the included studies were:

- Poorly defined patient selection criteria;
- Low statistical power;
- New patients and patients who had received ablative surgery on a previous occasion in the same study population;
- Mixed interventions (i.e. pooled results for pallidal and thalamic stimulation);
- Follow-up of patients was generally short: three months for blinded assessments and up to 12 months in unblinded studies;
- Losses to follow-up of study patients were common. In some papers, whether or not there was complete follow-up of study patients was impossible to determine as patient numbers were not given in the results. This omission is particularly important when considering those patients who withdrew from surgery and whose outcomes could have changed the conclusions of the study. For example, patients may have withdrawn from DBS because of adverse outcomes or ineffectiveness. Their absence from the analysis would therefore lead to an overestimation of the efficacy of treatment;
- Statistical precision in the form of p values and/or confidence intervals for differences in stimulator ON versus stimulator OFF was reported by only one study[62];
- Details regarding the duration of the stimulator ON and stimulator OFF cycles were absent, which may bias the results if the length of treatment differed between one intervention and the next; and
- None of the papers quantified the number of visits required to adjust stimulator settings for optimal effect or to reduce side effects. This information has major implication for cost-benefit analyses when comparing the difference between in-patient and out-patient treatment costs including patients' travelling expenses.

Although this review concluded there was insufficient good quality evidence to reach a conclusion on the efficacy of DBS, the results of four studies are worthy of discussion.[47, 63-65] These four studies were randomised controlled trials which compared Parkinson's disease symptoms for stimulator ON versus stimulator OFF. All studies used blinded evaluations for at least three months with patients randomised to stimulation OFF or ON.

The study by Kumar, Lozano et al[62] evaluated subthalamic DBS in a sample of six patients. The results of this study showed that at six months follow-up, a significant improvement in total UPDRS scores was observed for stimulator ON compared to stimulator OFF for both on and off medication (58 percent, $p=0.002$ and 49 percent, $p<0.01$ respectively). Stimulation ON also improved motor sub-scale item scores (tremor, bradykinesia, rigidity and postural stability and gait) when compared to stimulation OFF.

For medication on, statistically significant improvements were observed for bradykinesia, rigidity and postural stability and gait. However, no significant improvement was observed for tremor.

For medication off, statistically significant improvements were observed for all motor subset scores. It is important to note there were a number of operative complications which occurred in this study such as cortical venous thrombosis (n=1), mild reduction in verbal memory (n=1), postoperative confusion (n=2), mild personality change (n=1) and transient hemichorea (n=2). Transient paresthesiae with stimulation ON was also observed in two patients.

This was the only study that made comparisons between stimulator ON and OFF while patients were both on and off medication. However, with such a small sample size, it is possible the number of operative complications reported in the study could outweigh the benefits gained. If this were the case, this result could possibly be attributed to the investigators' lack of experience in this type of surgical procedure.

Other studies such as those by Koller, Pahwa et al[64] and Ondo, Jankovic et al[47] merely reported significant differences in the ON state versus OFF state without providing the mean or standard deviations as part of their results. The study by Koller, Pahwa et al[64] compared changes in tremor scores (from baseline) between two groups, treatment (thalamic stimulation ON) and controls (thalamic stimulation OFF) for 24 Parkinson's disease patients. The results of this study showed stimulation ON produced a significant decrease contralaterally in essential tremor and Parkinsonian tremor at three months blinded evaluation and six, nine and twelve months open evaluation. All other outcome measures were pooled for essential tremor and Parkinson's disease patients. Ondo, Jankovic et al[47] also reported significant improvement in ON versus OFF scores for contralateral arm ($p<0.05$) and leg tremor ($P<0.05$) in a sample of 19 patients receiving thalamic DBS. For pallidal stimulation, similar results were also observed, with the study by Galvesz-Jimenez et al[65] reporting a 33 percent improvement for total UPDRS motor scores at three months when compared to stimulator OFF results in four patients receiving GPi stimulation.

Controlled trials published since the DEC health technology assessments

All of the studies published since the DEC report have been case series. Since this study design did not meet the inclusion criteria and in light of higher level evidence presented in the above HTAs, these articles were not assessed.

Summary of findings

A conclusion regarding the effectiveness of DBS cannot be determined because of major methodological problems and poor quality of reporting in each of the studies used in the above HTAs. Although a number of studies support the effectiveness of pallidal, thalamic and subthalamic DBS in controlling Parkinson's disease symptoms, it is important to note that their results are subject to a number of serious limitations and therefore should be considered with extreme caution. More randomised-controlled studies of good methodological quality and reporting are needed. Studies that look at long-term effectiveness and take full account of patients' quality of life in addition to Parkinson's disease symptoms are still required in order to make a valid assessment of effectiveness. However, the difficulties in conducting evaluative research in this area need to be acknowledged. These include challenges in conducting RCTs in surgery (e.g. use of controls and differentiation between the intervention and surgeons' experience and competence in performing the procedure) and small patient numbers presenting at each centre.

Ongoing Primary Studies

The Internet sites searched for references to ongoing randomised controlled trials comparing DBS with ablative surgery or medical therapy included FDA, TrialCentral, Current Controlled Trials, National Research Register, Medical Research Council UK and National Parkinson's Foundation. Information regarding additional trials was also obtained from the literature.

Four trials purported to evaluate the efficacy of deep brain stimulation against ablative procedures. None of the trials has been published and contact with the primary investigators or their representatives did not result in any new information. This section presents the status of these studies as at 23 April 2001.

Kings Healthcare R&D consortium

Effect of unilateral and bilateral microelectrode-guided chronic subthalamic stimulation on motor and language function, neurotransmitter activity and regional brain activation in Parkinson's disease. Funded by the Parkinson's Disease Society (UK). Estimated date of completion - 31st October 2000.

University Hospital Birmingham NHS Trust

Sensory motor effect of surgical alleviation of tremor in Parkinson's disease. Funded by the Medical Research Council (UK). Estimated date of completion - 1st January 2004.

Central Sheffield University Hospitals NHS Trust

A randomised comparison of the effect of lesioning and deep brain stimulation on cognitive function and motor control in idiopathic Parkinson's disease. Funded by Medtronic. Estimated date of completion - 1st December 2001.

University College London Hospitals NHS Trust

A study of deep brain stimulation. Funding information not specified. Estimated date of completion - 1st December 2000.

What are the economic considerations?

General Framework

The framework for the economic evaluation of a medical technology considered by MSAC is the comparison of the costs and benefits of that technology compared with the current alternative treatment. Cost effectiveness analysis involves the calculation of an incremental cost effectiveness ratio $(C_I-C_c)/(O_I-O_c)$, where C_I is the total cost of resources used associated with the intervention, C_c is the total cost of resources used by the comparator, O_i is the outcome associated with the intervention, and O_c is the outcome associated with the comparator.

When there are two comparators, a weighted average of cost and outcome can be calculated where the weights are the proportion of patients who are likely to receive each of the comparator treatments. Given the uncertainty surrounding the effectiveness of deep brain stimulation (DBS) and the costs of establishing a treatment facility in Australia, data in this area of research are limited. Therefore, an exploratory cost analysis was all that could be undertaken. Cost data have been taken from a number of sources to predict the cost of DBS in Australia and to estimate the cost of alternative treatments.

Comparator

The specific question to be answered by this application is whether deep brain stimulation (DBS) is more effective than ablative surgery (thalamotomy or pallidotomy). Effectiveness is measured in terms of cost to the community to achieve relief of symptoms associated with severe Parkinson's disease (PD) and an improved quality of life for Parkinson's patients.

Costs

DBS is a more complex technological procedure than ablative surgery and is likely to be more expensive. The costs of bilateral pallidotomy (or subthalamotomy) using the Australian data provided in the MSAC application is $2,686. The cost of bilateral DBS was stated as $26,245. The breakdown of the latter figure can be seen in Table 15.

Table 15 Cost components of DBS, as stated in MSAC application

Component of the service	Cost ($)
Neurosurgical procedure, two leads	2,000
Complex mapping procedure, two leads	2,000
Assessment procedure	500
Implantation of two neurostimulators	524
Anaesthetic associated with the implantation of two neurostimulators	131
Neurostimulator programming two neurostimulators	500
Cost of implantable equipment for bilateral implant	20,590
Total additional cost	26,245

These figures give us a cost difference between the procedures of $23,559. For 60 additional procedures this would suggest an additional cost of $1.41 million, and for an extra 250 procedures additional costs of $5.89 million. For the quoted numbers of patients who would potentially benefit from the procedure immediately, costs range from $16.49 million (700 patients) to $70.68 million (3,000 patients). Given these are procedural costs only, excluding for example, follow-up costs, they are likely to be underestimated.

A Health Technology Assessment (HTA) has been undertaken in the UK for pallidotomy, thalamotomy and DBS for severe PD, making use of more comprehensive data[3]. Costs from the HTA report are summarised in Table 16, (converted from UK£ to A$ at a rate of 2.46A$ to 1UK£, see Appendix E). It is anticipated that estimates for bilateral procedures would be much greater.

Table 16 UK price tariffs (converted to A$) for unilateral pallidotomy, thalamotomy and DBS (with in-patient follow-up)[a,b]

	Pallidotomy	Thalamotomy	DBS (including device)
Total costs of the intervention (including pre-operative assessments in some cases)			
Min.	$ 16,580	$ 16,580	$ 31,340
Max.	$ 27,060	$ 27,060	$ 35,547
Cost of follow-up appointments			
Min.	$ 172	$ 172	$ 172
Max.	$ 343	$ 343	$ 343
Min. no. of follow-up appointments	4	4	4
Annual follow-up appointments	$ 1,431	$ 1,431	$ 1,431
Cost per in-patient follow-up (stimulator adjustment)			
Min.	n/a	n/a	$ 7,380
Max.	n/a	n/a	$14,760

a Note that the National Hospital Cost Data for 1996/97 suggest an average cost for a craniotomy with complications (DRG 23) in a public hospital of $16,996. To the extent that this is a procedure of similar intensity the minimum estimates in Table 1 may be a reasonable reflection of resource use in Australia.

b Note these are extra contractual referral tariffs, which may be interpreted as prices rather than costs, but are usually calculated in a manner to cover costs as the UK NHS is a public service.

Pallidotomy and thalamotomy are one-off procedures. DBS involves the activation of a device to stimulate areas of the brain and may require adjustment over a number of years, as well as battery replacement. The ablative procedures and DBS have similar work-ups. For DBS it is difficult to quantify how many visits are required for adjustment of the Implantable Pulse Generator (IPG) settings to maximise benefit. For some patients this may be considerable, with a visit every three months. Battery changes are also required every three to five years requiring implementation of a new IPG. One difference in Australia is that the stimulator adjustments are undertaken as an outpatient procedure. The following estimates reflect this.

Over a five-year period, costs could range from $24,423 to $35,587 for ablative surgery (see Table 17) and $53,417 to $60,808 for DBS (see Table 18). Over a five-year period marginal costs could range from $17,830 to $36,385. For a minimum projected number of patients (60 per year) this would mean potential additional costs of between $1 and $2.1 million over a five-year period for these 60 patients. If the maximum number of patients were limited to 250, this figure could reach $4.5 to $9.1 million for the same period.

Table 17 Five year costs for ablative surgery (converted from UK costs)

	Minimum costs ($)	Maximum costs ($)
Intervention	16,580	27,060
Follow-up (4 appointments)	688	1,372
Annual follow-up (5 appointments)	7,155	7,155
Total costs	24,423	35,587

Table 18 Five year costs for DBS (converted from UK costs)

	Minimum costs ($)	Maximum costs ($)
Intervention	31,340	35,547
Follow-up (4 appointments)	688	1,372
Annual follow-up (5 appointments)	7,155	7,155
Stimulator adjustment (1 per year)	2,500	5,000
New battery	11,734	11,734
Total costs	53,417	60,808

If bilateral procedures were undertaken, or DBS follow-up admissions were higher (the figures above are based on a conservative estimate of one adjustment per year), then costs would increase substantially. For example, if there were a more realistic four visits per year for stimulator adjustment, costs for DBS would increase to between $60,917 and $75,808 (see Table 19). Marginal costs would thus increase to between $25,330 and $51,385. This would increase potential additional total costs to between $1.5 and $3.1 million for 60 patients, and between $6.3 and $12.8 million for 250 patients.

Table 19 Five year costs for DBS (higher follow-up estimate) (converted from UK costs)

	Minimum costs ($)	Maximum costs ($)
Intervention	31,340	35,547
Follow-up (4 appointments)	688	1,372
Annual follow-up (5 appointments)	7,155	7,155
Stimulator adjustment (yr 1, 4 visits per year)	2,500	5,000
Stimulator adjustment (yr 2-5, 4 visits per year)	7,500	15,000
New battery	11,734	11,734
Total costs	60,917	75,808

However, this is only one side of the argument[3]. There may also be potential cost savings following successful neurosurgery, although these are difficult to quantify in monetary terms. Health services expenditure may be lower because there could be:

- a reduction in the treatment of the consequences of Parkinson's disease, such as falls;
- reduced medication costs (for example $2,460 a year for apomorphine and $3,690 if a dopamine agonist could be stopped);
- increased savings in medical equipment (for example wheelchairs), hospitalisation and rehabilitation costs;
- fewer community nursing and GP consultations;
- reduced call on paramedic and other ambulance services; and
- less need for therapy (physio, occupational, speech).

There may be further cost savings for individuals and carers in terms of time and loss of earnings, home modifications, patients' purchase of equipment (for example wheelchairs), transport and other intangibles concerning quality of life. Savings to the social service and community health sectors may include residential care/nursing, social worker assistance, community assistance (for example the provision of meals) and home modifications. These savings are largely unquantifiable and could be significant. For example, there could be savings of up to $40,000 in residential care if either procedure were effective. However, there is no evidence in the literature referred to in this report of any substitution of drug treatment, and costs of care may remain the same given the lack of evidence on the effectiveness of the procedure.

Overall costs of treatment for PD including the need for more adjunctive drugs increase as the disease progresses. Data from the UK put costs at UK£92.5 million.[3] Given the relative size of the populations, this would imply a cost of approximately $73 million per year for Australia. This figure is made up of 70 percent hospital care, 14 percent primary care and 16 percent for drugs. However, the direct costs of PD may be a small portion of the overall burden because indirect costs may be high.

Outcomes

A review of the literature found only one paper with useable outcomes data from a randomised controlled trial[6] The outcome used here to assess cost-effectiveness is based on outcomes data from Schuurman, Bosch et al[6] which looks at changes in functional status as measured by the Frenchay Activities Index[68]. This assesses 15 daily life activities involving domestic tasks (preparing meals, washing clothes and dishes, general housework), leisure or work activities (social events, hobbies, reading, working) and outdoor activities (shopping, walking, gardening). Activities are measured on a four-point scale and scores can range from zero to 60. An increase of four points indicates an improvement in a patient's ability to perform at least two activities. An increase of five points is said to be associated with a clinically relevant improvement in the ability to perform daily life activities.

Schuurman, Bosch et al[6] found, for 45 PD patients randomised to either thalamotomy or DBS, thalamotomy patients had a mean change in score of 0.8 (+/- s.d. 4.9) while the DBS patients had a mean change in score of 5.5 (+/-s.d. 6.3). This represents a difference between the groups of 4.7 (95% CI 1.2-8.0) and this suggests DBS may have some impact on a patient's ability to undertake everyday living.

Incremental Cost-effectiveness

Based on the Australian data in the MSAC application, the extra cost of a 4.7 change in the Frenchay scale would be $23,559. This is probably an underestimate of actual costs because it is based on procedural costs only and does not account for multiple follow-ups and battery changes.

If the wider range of costs suggested here are combined with the effectiveness data from the literature, the incremental cost effectiveness of DBS compared to ablative surgery can be estimated. Based on the UK cost data for a 4.7 point improvement on the Frenchay scale, there is an extra cost of between $17,830 and $51,385. However, the value patients would put on this gain in terms of preferences is not clear. Therefore it is difficult to say if the procedure is cost effective given the high costs for a small increase in some aspects of quality of life measured by this scale. The costs noted here are over a five-year period since DBS requires follow-up procedures. Since the follow-up time used in these calculations was only six months, it is assumed here that follow-up adjustments would at least maintain the difference in the levels of daily function between the two patient groups (ablative and DBS) over the five-year period. This may not be a reasonable assumption.

Conclusions

The evidence available does not allow a definite estimate of the cost effectiveness of DBS as compared to ablative surgery in the treatment of severe PD. Estimates provided here suggest an incremental cost of at least $23,559 (application cost data), but more likely between $17,830 and $51,385 over five years, for a small change in ability to undertake daily tasks. However, it should be noted the effectiveness suggested here is based on one study and costs are based on UK data. Whichever cost structure is used, the costs for DBS are greater than current ablative techniques.

While there is no evidence ablative surgery or DBS increases length of life for patients with severe PD, there would appear to be some evidence DBS may improve some aspects of quality of life (in terms of some simple daily tasks) during the first six months[6]. If this continued over a number of years (and there is no evidence this would happen) then there may be a case for measuring the improvement in QALYs. If daily function was maintained with DBS, allowing for further interventions to adjust electrodes and maximise potential functional activity gains, then DBS may provide an advantage over ablative surgery. If so, then in cost per QALY terms, DBS may be acceptable (the extra costs over ablative surgery are estimated to be in the range of $17,830 to $51,385 per patient). Given that these procedures are generally undertaken only after patients have become unresponsive to drug therapy, measuring the quality of life of patients is vital in determining their suitability for DBS.

However, at this stage it is not possible to establish whether or not DBS offers substantial improvements in quality of life over the long-term.

Conclusions

Safety

Adverse effects resulting from deep brain stimulation varied with the target site. They were generally reported to be mild and reversible, often improving when the level of stimulation was reduced. However, more serious events such as death and haemorrhage have been associated with the procedure. The majority of the adverse effects presented in the papers were short-term outcomes (three to twelve months post-surgery). Therefore a clear need for a long-term study of safety is required.

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

Effectiveness

Thalamic stimulation compared to thalamotomy

A single high-quality randomised controlled trial was identified which provided some evidence that, six months after surgery, thalamic stimulation significantly improved some aspects of quality of life when compared to thalamotomy.

Pallidal stimulation compared to pallidotomy

A single randomised controlled trial reported that pallidal stimulation and pallidotomy were not significantly different in ameliorating Parkinson's disease symptoms three months after surgery. However, this study was limited by its research methodology which included small sample size and lack of clarity in length of follow-up.

Sub-thalamic stimulation compared to ablative surgery

No studies were identified which statistically compared the effect of sub-thalamic stimulation with ablative surgery in Parkinson's disease patients.

In order to prove DBS (pallidal, thalamic and sub-thalamic) is more effective than ablative surgery, more rigorous study and reporting showing both long- and short-term effectiveness is required.

DBS compared to medical therapy

Based on the results of two health technology assessments (HTAs) it would appear some studies have shown DBS (thalamic, subthalamic and pallidal) is more effective than medical therapy. However, any conclusions regarding the effectiveness of DBS over medical therapy cannot be determined because major methodological problems and poor quality of reporting were apparent in each of the studies reviewed here. More randomised controlled studies which look at long-term effectiveness and take full account of patients' quality of life as well as Parkinson's disease symptoms are still required in order to make a valid assessment of effectiveness.

Cost-effectiveness

The paucity of evidence comparing DBS with ablative surgery in PD patients makes it impossible to establish whether DBS offers substantial improvements in quality of life over the long-term. Estimates suggest costs for DBS are between $17,830 and $51,385 per patient greater than current ablative techniques.

One study showed thalamic DBS may improve some aspects of quality of life for PD patients when compared to thalamotomy. If daily function could be maintained with DBS, allowing for the adjustment of electrodes and maximising potential functional activity gains, then it may offer an advantage over ablative surgery. However, more studies demonstrating its long-term effectiveness are required.

Recommendation

MSAC recommends that, based on the strength of evidence pertaining to deep brain stimulation for Parkinson's disease (MSAC application no. 1031), interim public funding should be supported:

- for patients where their response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; and
- subject to patients' participation in an appropriate controlled trial to obtain information on adverse events, longer-term patient outcomes and costs in the Australian setting. This should be carried out in consultation with appropriate groups and States, and should be limited to centres with necessary expertise.

This recommendation is to be reviewed no later than three years from the date of this report.

The Minister for Health and Aged Care accepted this recommendation on 19 June 2001.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Commonwealth 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 Commonwealth 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 Commonwealth Minister for Health and Ageing on references relating either to new 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 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**
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	internal medicine
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	Paediatrics
Dr David Robinson	plastic surgery
Professor John Simes	clinical epidemiology and clinical trials
Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council

Appendix B Supporting committee

Supporting committee for MSAC Application 1031 - Deep brain stimulation for the symptoms of Parkinson's disease

Professor Bryant Stokes (Chair) MBBS, FRACS Chief Medical Officer Health Department of Western Australia	member of MSAC
Dr David Jarvis MBChB, FRACGP, BA, BLitt General Practitioner	nominated by the Royal Australian College of General Practitioners
Dr Kate D'Este Dip Appl Sc, BMath, Dip Ed, Dip Med Stats, PhD Senior Lecturer in Biostatistics Faculty of Medicine and Health Sciences University of Newcastle	co-opted epidemiologist and biostatistician
Professor Philip Thompson MBBS, PhD, FRACP Director of Neurology, Royal Adelaide Hospital	nominated by the Australian Association of Neurologists
Professor Robert Helme MBBS, PhD, FRACP Consultant Neurologist Western Hospital, Footscray	nominated by the Australian Society for Geriatric Medicine
Mr Peter Dawkins Chief Executive Officer, Parkinson's Australia	consumer representative nominated by the Consumers' Health Forum of Australia
Dr Malcolm Pell MBBS, FRACS Neurosurgeon Saint Vincent's Hospital, Sydney	co-opted neurosurgeon

Appendix C Studies included in the review

Studies comparing DBS with ablative surgery

First Author and Year of Publication	NHMRC Level of Evidence	Study Design	Location	Dates of Enrolment	Characteristics of Study Population		
					Size	Age (in years)	Sex Ratio (M:F)
Schuurman (2000)[6]	II	RCT	Netherlands	June 1995 to Oct 1998	T-DBS=22 T=23	T-DBS=63±8.9[a] T=68±7.9[a]	Not stated
Merello (1999)[60]	II	RCT	Argentina	Not stated	P-DBS=6 P=7	P-DBS = 59.1±6.4[a] P=55.3±9.8[a]	P-DBS=4:2 P=5:2
Tasker (1998)[35]	III-2	Retrospective cohort	Canada	November 1990 to July 1996	T-DBS=19 T=26	T-DBS 26% 30-40 yrs 42% 51-70 yrs 32% >70 T 19% 30-40 yrs 69% 51-70 yrs 12% >70	T-DBS= 15:3 T=16:13
Tasker (1997)[61]	III-2	Retrospective cohort	Canada	1990-1995 (only years reported)	T-DBS=13 T=23	Data was pooled for PD, essential tremor and multiple sclerosis patients	Data was pooled for PD, essential tremor and multiple sclerosis patients

a Mean ± standard deviation

Abbreviations: T-DBS = Thalamic DBS group; P-DBS = Pallidal DBS group; T = Thalamotomy group; P = Pallidotomy group; M = male; F = female

Studies comparing DBS with medical therapy (medication on/off or stimulation off)

First Author and Year of Publication	NHMRC Level of Evidence	Study Design	Study population	Intervention	Comparator	Study design of included trials
Nicholson (1999)	I	Rapid Review	Severe Parkinson's disease patients refractory to drug treatment	Deep Brain Stimulation - Pallidal, Thalamic, Subthalamic	Usual care or placebo (stimulation turned OFF)	Cross over randomised studies, which used blinded outcome assessments. (n=5)

Appendix D Staging and rating scales used for Parkinson's disease

Hoehn and Yahr Staging of Parkinson's Disease[69]

Stage	Symptoms
I	Signs and symptoms on one side only, symptoms mild and inconvenient but not disabling. Usually present with tremor of one limb. Friends have noticed changes in posture, locomotion and facial expression.
II	Symptoms are bilateral, minimal disability, with posture and gait affected
III	Significant slowing of body movements, early impairment of equilibrium on walking or standing, generalised dysfunction that is moderately severe
IV	Severe symptoms, but can still walk to a limited extent, rigidity and bradykinesia, no longer able to live alone, tremor may be less than earlier stages.
V	Cachetic stage, invalidism complete, cannot stand or walk, requires constant nursing care

United Parkinson's Disease Rating Scale[70]

The UPDRS is a rating scale for Parkinson's disease. It is divided into four sub-scales as shown in the table below. This instrument is administered by interview and its scores range form 0=no disability to a maximum of 199=worst disability. An overall score is produced by combining sub-scales II and III. In all sub-categories the higher the score the worse the disease severity.

Sub-scale	Description	Maximum score
I	Mental, behaviour and mood	16
II	Activities of daily living (ADL) in 'on'[a] and 'off'[b] states	52
III	Motor examination in 'on' and 'off' states	108
IV	Part A Dyskinesia	13
	Part B Clinical fluctuations	7
	Part C	3

a 'off' state = evaluation at 8-9 hours after = 12 hours withdrawal from drug therapy
b 'on' state = evaluation when optimally medicated

Frenchay Activities Index[68]

The FAI is comprised of 15 items, each of which measures an activity that requires some decision making and organising on the part of the patient both at home and outside the home. The instrument consists of a single score that can range from 15 to 60. It can also be divided into three sub-scale scores: domestic, leisure/work and outdoors. For the FAI the higher the score the better the functional status of the patient. It is important to note however, that the FAI is not a Parkinson's disease-specific instrument.

Appendix E Conversion to Australian dollars

The relative proportion of total health expenditure as a proportion of Gross Domestic Product (GDP) is used to approximate the cost components in terms of relative cost in Australia, and then converted to Australian dollars at purchasing power parity (PPP). Total health expenditure as a proportion of GDP in Australia is 8.6 percent. Health expenditure as a proportion of GDP in the UK is 6.9 percent. Therefore, an estimate of the relative health costs for Australia : UK is 8.6 : 6.9 (a relative index of 1.25 used to convert UK costs to costs in Australia).

The PPP for GDP for Australia : UK is 1.31 : 0.664. Therefore, UK costs are multiplied by 1.97 to convert the UK costs to Australian dollars. Overall, to convert UK health care costs to Australian dollars, costs are multiplied by 2.46 (1.25 x 1.97).

Abbreviations and Definitions

ADL	Activities of Daily Living
Akinesia	Absence or poverty of movement associated with a sharp decline in motor performance
Bradykinesia	An abnormal slowness of movement
CAPIT	Core Assessment Program for Intracerebral Transplantation
CI	Confidence Interval
Contralateral Side	Affecting the opposite side of the body
DBS	Deep brain stimulation
Dyskinesias	Involuntary movements comprising dystonia, athetosis and chorea occuring during therapy with levodopa in patients with Parkinson’s disease
Freezing	Freezing of movement, with inability to resume movement, particularly gait (walking)
Frenchay Activities Index	Instrument used to measure disability and handicap (Appendix D)
Gait	Pattern of walking. Parkinson's disease patients may experience walking difficulties where gait is usually slow with short steps
Gpi	Globus pallidus (internal or medical segment)
Hoehn & Yahr scale	A system for rating severity of Parkinson's disease (Appendix D)
HTA	Health Technology Assessment
Ipsilateral	Affecting the same side of the body
Motor fluctuations	Fluctuations in patients' motor functions, usually arising when the effect of a drug such as levodopa begins to wear off. Usually patients fluctuate from being 'on' and mobile to being 'off' and immobile
NS	Not significant
Off state	Motor state after 12 hours without anti-Parkinsonian drug (immobile)

On state	Motor state while taking anti-parkinsonian drug (mobile)
Off time	Duration of immobility
On time	Duration of mobility
ON and OFF	ON refers to stimulator on and OFF stimulator off in contrast to drug related 'on' and 'off' states
Parkinsonism	Signs and symptoms seen in Parkinson's disease such as tremor and muscular rigidity.
PD	Parkinson's disease
Postural instability	Impaired balance and co-ordination. As a result patients develop a forward or backward lean and fall easily
PVP	Posteroventral Pallidotomy (target within medial globus pallidus)
Refractory	Not readily yielding to treatment
RCT	Randomised Controlled Trial
Rigidity	Stiffness or inflexibility of the limbs and trunk
SD	Standard deviation
Stereotaxy	The mathematical discipline of calculating angles and distances from outside the brain to a chosen point with in the brain. These calculations can be performed with or without the use of a frame
STN	Sub-thalamic nucleus
Tremor	Involuntary trembling or quivering which can effect the hands, arms, legs, jaw, and face
UPDRS	Unified Parkinson's disease rating scale (Appendix D)
VIM	Ventral intermediate nucleus of the thalamus
WAIS	Wechsler Adult Intelligence Scale

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