NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease)

Essential tremor (involuntary shaking of one or both hands) and dystonia (abnormal muscle spasm) can affect movement and posture. They can be treated by stimulating of a precise area of the brain using an electrode.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in February 2006

Procedure name

Deep brain stimulation - DBS

Specialty societies

- Association of British Neurologists
- Society of British Neurological Surgeons

Description

Indications

Tremor and dystonia are symptoms arising from a number of different neurological diseases other than Parkinson’s Disease, including Essential Tremor, Multiple Sclerosis and Primary Generalised Dystonia.

Tremor is an involuntary rhythmic repetitive movement, most frequently affecting the upper limbs. Tremor can occur at rest, or be brought on (or

exacerbated) by posture or intentional movement. Severe tremor can be disabling as it affects fine movement coordination.

Dystonia describes uncoordinated simultaneous contraction of both opposing agonist and antagonist muscles. As a condition it can be focal and limited to a particular group of muscles, or be generalised.

Current treatment and alternatives

Currently available conservative management options for dystonia do not cure the underlying neurological disorder but improve symptoms. Over time, the severity of dystonia progresses as part of the underlying neurological condition. Surgical options include thalamotomy or pallidotomy however symptoms may relapse typically over some months and benefits may not be maintained in the long-term.

Most patients with tremor may benefit from rehabilitation and drug therapy and early appropriate treatment may minimise functional disability. Anti-tremor drugs such as propranolol or primidone exert their ameliorating effects by reducing tremor amplitude without any effect on frequency. A reduction in tremor amplitude, does not, however, always translate into functional improvement. Surgery, commonly involving surgical ablation of the thalamic nucleus, is usually reserved for patients with severe disabling tremor and functional disability that interferes with activities of daily living; or tremor that is refractory to the highest tolerated doses of medication..

What the procedure involves

Deep brain stimulation can be carried out on structures within the brain that are responsible for the modification of movements, such as the thalamus, the globus pallidus and the subthalamic nucleus, that interact functionally with the substantia negra (nigra). Each of these structures is bilateral, in the left and right hemispheres, surgery may therefore be carried out on one or both sides. Deep Brain Stimulation alters, through the application of electrical current, the function of these brain nuclei.

The procedure involves inserting fine needles into the brain through small holes made in the skull to determine the exact position of the nucleus, which may be different in each patient. This part of the procedure is usually carried out under local anaesthetic. A permanent electrode is then placed into this nucleus. Under general anaesthetic this wire is then tracked down subcutaneously to the anterior chest wall, where it is connected to a pulse generator .

Efficacy

Tremor

A case series study included in a systematic review found that there was an improvement in total tremor score in up to 27 months follow-up, although there was no significant improvement in most other efficacy outcomes[1]. ,. Conversely, four case series included in the same systematic review reported on functional ability all reported improvements in activities of daily living following deep brain stimulation[1]. A case series of 52 patients with essential tremor having deep brain stimulation found a significant improvement in activity of daily living at 3 months follow–up, with scores improving from 17.8 points to 6.5 points ($p < 0.001$)[2]. Another case series of 19 patients found that deep brain stimulation produced an improvement in tremor score (Fahn-Tolosa-Marin scale) from 3.3 points at baseline to 0.8 points at 27 months follow-up ($p < 0.005$)[3].

Overall there were very few data available relating to the use of deep brain stimulation for multiple sclerosis. Three case series reported significant improvements in tremor at 12 to 22 months, however two studies found that improvements in tremor did not necessarily correlate with improvements in functional ability[1].

Dystonia (including Primary Generalised Dystonia)

Data included in a systematic review of deep brain stimulation in dystonia showed marked improvements in clinical severity of dystonia as evaluated on the Burke-Fahn-Marsden Dystonia Rating Scale, with scores improving from baseline values by between 34% and 88%, although some of these differences were not statistically significant[1].

A case series of 22 patients having deep brain stimulation found that total Burke-Fahn-Marsden Dystonia Rating Scale score improved significantly from baseline 46.3 points to 24.3 points at 3 months follow-up, and this effect continued through to 12 months when the score was 21.0 points ($p < 0.001$ for both comparisons to baseline). Similarly, global disability score improved from 11.6 points at baseline to 7.6 points at 3 months, and 6.5 points at 12 months follow-up ($p < 0.001$)[4].

Another 22 patients undergoing deep brain stimulation for dystonia found a significant improvement in quality of life with scores improving from 29 points at baseline to 76.2 points at 25 months follow-up ($p < 0.01$)[5].

Safety

One case series reported that pulse generator failure occurred in 50% (6/12) of patients having deep brain stimulation, but the cause of this failure is not described[6]. Other device-related complications reported include stimulating electrode displacement, which sometimes required further surgery. Across the case series where this outcome was reported this occurred in 6% (1/18)[3], 8% (1/12)[6] and 15% (8/52)[2] of patients. The incidence of lead fracture or failure varied across studies: 4% (2/52)[2], 5% (1/22)[4] and 6% (1/18)[3].

One case series of 22 patients undergoing deep brain stimulation for dystonia found that there was one case each (5%) of transient oedema of the frontal lobe, cutaneous necrosis of the scalp, localised skin infection, and haematoma at site of the electrode. However, none of these events had permanent sequelea[4].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to Interventional procedure overview of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). Searches were conducted via the following databases, covering the period from their commencement to 20 February 2006. MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with essential tremor or dystonia
Intervention/test	Deep brain stimulation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on one systematic review of controlled studies and case series of patients with essential tremor, dystonia, and multiple sclerosis[1], and five case series; three concerning patients with dystonia[4,6,5] (one of children with dystonia[6]) and two concerning patients with essential tremor[2,3].

Existing reviews on this procedure

The Trent institute for health care research have produced an evidence-based commissioning collaboration report, which is detailed in Table 2[1]. This report includes data from the 2001 Wessex Institute for Health Research and Development report.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

IPG019 Deep brain stimulation for Parkinson's disease
http://www.nice.org.uk/page.aspx?o=91583

Technology appraisals

None

Clinical guidelines

Parkinson's disease – Second consultation, due June 2006
http://www.nice.org.uk/page.aspx?o=33924

Public health

None

Table 2 Summary of key efficacy and safety findings on deep brain stimulation for tremor and dystonia (excluding Parkinson's disease)

Abbreviations used: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; PGD, primary generalised dystonia; CD, cervical dystonia; MMSE, Mini-Mental State Examination; ADL, activities of daily living; EQ-5D, Euroquol; TWSTRS – Toronto western spasmodic torticollis rating scale; SF-36 – short form health survey

Study Details	Key efficacy findings	Key safety findings	Comments
Denby T (2004)[1] **Systematic review** UK 13 studies (1 systematic review and 12 case series) were identified that evaluated the effectiveness of DBS for patients with dystonia, 12 studies (1 systematic review, 1 RCT, 2 case control studies, and 8 case series) for patients with essential tremor, and 4 (1 systematic review and 3 case series) for patients with multiple sclerosis. n = >200+ with dystonia (% primary and secondary dystonia varied between studies), >300 with Essential Tremor, and 72 with MS. Follow-up = 3 months to 6.5 years	**Dsytonia** Primary generalised dystonia: There were marked improvements in the clinical severity of dystonia, following DBS, as assessed by BFMDRS. Improvement in scores, from baseline to last follow-up, ranged from 34% to 88%. Some of these improvements were statistically significant. Functional score of BFMDRS improved by 27% to 95%. Two studies found that DBS was as effective for children as adults, with no significant difference between children and adults in the functional or clinical score following surgery. In four studies of patients with cervical dystonia, mean improvements in severity on the TWSTRS were around 63%, in disability they were between 60% and 69% and in pain 50% and 59%. Secondary dystonia (definition not stated): The evidence indicates that these patients respond less favourably to DBS than PGD or CD. Across three studies, the improvement in BFMDRS clinical scores following surgery were 12% at 3 months, 14% at 6 months, 31% at 1 year and 23% at 2 years. Functional BFMDRS score assessed in one study had improved by just 7% at 1 year and 9% at 2-year follow-up. In one study patients reported better performance and more independence but no significant change was found in the formal assessment of their disability. One study evaluating the effects of DBS on patients suffering from PGD or segmental dystonia reported a significant improvement in quality of life of 64%, as measured by EuroQol1 6–12 months after surgery. Another study assessing the effects of DBS on PGD patients reported an	**Complications** Adverse events were common and similar across all patient groups, and included surgical complications, stimulation side effects, infection and device related problems. Very few studies gave estimates given on the numbers or rate of adverse events per patient or subgroup. Instead, descriptions of the type of incidents suffered across the whole study population were common. There were few reported surgical complications. In contrast, side effects associated with stimulation, such as transient paraesthesia, were common, although were considered mild and were often controlled with changes in stimulation parameters. Device-related complications were also common and included infection, lead fractures, sudden battery depletion and lead slippage. These adverse events were potentially more serious, and in some cases led to repeat surgery. In one case-control study comparing thalamotomy and DBS, thalamotomy resulted in a higher level of surgical complications. A larger number of DBS patients, however, underwent repeat surgeries due to hardware complications.	Thorough literature search and study selection A 'rebound phenomenon' was reported in a few studies evaluating the effect of DBS on dystonic patients where sudden cessation of stimulation, as a result of hardware failure, led to acute severe relapse

Abbreviations used: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; PGD, primary generalised dystonia; CD, cervical dystonia; MMSE, Mini-Mental State Examination; ADL, activities of daily living; EQ-5D, Euroquol; TWSTRS – Toronto western spasmodic torticollis rating scale; SF-36 – short form health survey

Study Details	Key efficacy findings	Key safety findings	Comments
	improvement in health status, as measured by SF-36 by an average of 36% 3–12 months following surgery.		

Abbreviations used: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; PGD, primary generalised dystonia; CD, cervical dystonia; MMSE, Mini-Mental State Examination; ADL, activities of daily living; EQ-5D, Euroquol; TWSTRS – Toronto western spasmodic torticollis rating scale; SF-36 – short form health survey

Study Details	Key efficacy findings	Key safety findings	Comments
Denby T (2004)[1] continued	The two studies evaluating mental health found no significant changes in MMSE scores. In one study there was a significant fall in the level of depression 2 years after surgery, although this finding was not replicated in another study. **Essential Tremor** The case-control study that compared thalamotomy with DBS found no significant differences between any efficacy outcome variable over 27 months, although there was an improvement in total tremor score. In a very small case-control study (six patients) DBS modified several features of the tremor and reduced tremor severity. Only one of the patients still had a tremor with stimulation on, although the amplitude was considerably reduced compared with off stimulation The six case series reporting tremor severity all reported some level of improvement following DBS, four of which noted significant effects. In four of the case series reporting functional ability in this review, tremor ADL scores, derived from tremor severity rating scales, were detailed. All patients reported improvements in ADL following DBS. In a 12-month study, it was found that DBS improved the emotional condition of the patients and reduced the negative impact of the disease on their social life and life as a whole. **Multiple Sclerosis** Three case studies reported significant improvements in tremor at 12–22 months Two studies reported that the improvement in tremor didn't correlate with an improvement in functional ability or in patients' perception of their condition. In another case series patients reported that their ability to feed themselves was significantly improved 2 months after surgery, although at 1 year this was no longer statistically significant. One study reported quality of life based on SF-36. There were no significant changes following DBS		

Abbreviations used: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; PGD, primary generalised dystonia; CD, cervical dystonia; MMSE, Mini-Mental State Examination; ADL, activities of daily living; EQ-5D, Euroquol; TWSTRS – Toronto western spasmodic torticollis rating scale; SF-36 – short form health survey

Study Details	Key efficacy findings	Key safety findings	Comments
Vidailhet M (2005)[4] **Case series** France n = 22 (primary generalised dystonia) Cases with clinically diagnosed primary generalised dystonia with absence of secondary cause Leads were implanted bilaterally and attached at the posterolateral ventral part of the internal globus pallidus, with 4 contacts. The voltage and pulse width were adjusted according to clinical effect. Age = 30 years, male = 50%, median duration of disease = 18 years, DTY1 mutation n = 7. 20 cases were on medical treatment at baseline and 18 at final follow-up Follow-up = 1 year Declaration of interests: Supported by a grant from the Direction Regionale de la Recherche Clinique Assistance Public, and a grant from a manufacturer.	**Motor function** BFMDRS – total: Baseline 46.3; 3 months 24.6; p < 0.001; 12 months 21.0; p < 0.001 Global disability score: Baseline 11.6; 3 months 7.6; p < 0.001; 12 months 6.5; p < 0.001 In two patients motor symptoms worsened; these patients had severe tonic abnormal postures at baseline. BFMDRS subscores of face movement speech and swallowing did not improve significantly at any follow-up None of the baseline factors of sex, age, disease duration, DTY1 status, or BFMDRS score were significant predictors of outcome. In 20 cases assessed for on and off stimulation at 3 months, the total score for the BFMDRS was significantly worse with stimulation off than on: 34.6 and 24.6, respectively ($p < 0.001$). Scores when stimulation was off did not revert to baseline levels. **Quality of life** SF-36 general health: Baseline 47; 12 months 63; p 0.04 MMSE: Baseline 28; 12 months 28; p 0.33 Beck depression inventory: Baseline 11; 12 months 8; p 0.15	**Adverse events** There was one episode each (5% [1/22]) of transient postoperative oedema of the frontal lobe, fractured lead, cutaneous necrosis of the scalp, localised skin infection, and haematoma near the neurostimulator. All adverse events resolved rapidly without permanent sequelae.	Independent outcome assessment by videotape of cases wearing a hat to ensure blind evaluation. Outcome assessment at 3 months was done with the stimulator both on and off. 10-hour washout period may have been insufficient. Two cases required stimulation being reinstated during washout due to clinical deterioration. These cases were excluded from analysis. Authors note that there is a lack of standard criteria for classifying dystonia. No details given of method of patient recruitment. Multicentre study with each centre submitting a small number of cases may have resulted in some degree of operator inexperience.

Abbreviations used: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; PGD, primary generalised dystonia; CD, cervical dystonia; MMSE, Mini-Mental State Examination; ADL, activities of daily living; EQ-5D, Euroquol; TWSTRS – Toronto western spasmodic torticollis rating scale; SF-36 – short form health survey			
Study Details	**Key efficacy findings**	**Key safety findings**	**Comments**
Yianni J (2005)[5] **Case series** UK and Australia n = 22 (dystonia unspecified) No definition given of study cohort characteristics Electrodes inserted into the target area of the brain Outcomes were assessed using the EQ-5D questionnaire, with patient self-reporting Follow-up = 25 months Disclosure of interest: supported by a grant from the medical research council.	**Quality of life** There was a significant improvement in the EQ-5D scores following DBS at final followtup of 25 months. The score rose from 29 to 76.2 points ($p < 0.01$) **Willingness to pay** Patients willingness to pay for the operation ranged from £1000 to £1,000,000, with a mean price of £291 231 and a median price of £20,000.	No safety outcomes were reported	All operations undertaken by one surgeon. Study provides a cost–utility analysis of DBS. Willingness to pay outcomes may overstate the value of the treatment as individuals who respond well to the treatment may not recognise the wider range of benefits gained by others. Authors state that increased experience may improve patient selection for the procedure and result in better outcomes. Clinical benefits may enable some patients to return to work.

Abbreviations used: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; PGD, primary generalised dystonia; CD, cervical dystonia; MMSE, Mini-Mental State Examination; ADL, activities of daily living; EQ-5D, Euroquol; TWSTRS – Toronto western spasmodic torticollis rating scale; SF-36 – short form health survey

Study Details	Key efficacy findings	Key safety findings	Comments
Zorzi G (2005)[6] **Case series** Italy n = 12 (dystonia both primary and secondary) Cases from 1999 to 2003 Childhood-onset dystonia Positioning using MRI and (with general anaesthesia) bilateral electrode implant into the ventroposterolateral globus pallidus internus, with quadripolar electrodes. Stimulation started 2 days after surgery and adjusted during the first year to obtain the best response without side effects. Age = 15 years, Male = 83%, age of dystonia onset = 3.9 years, primary dystonia n = 7, secondary dystonia n = 2, status dystonicus n = 3, DTY1 mutation n = 1. Follow up = 1.8 years Disclosure of interest: supported by the national ministry of health and the Paolo Zorzi Association for Neuroscience.	**Motor responses** For 9 primary and secondary dystonia patients BFMDRS severity: Baseline 62 ± 17.8, Final evaluation 33.8 ± 20.1 BFMDRS disability: Baseline 16.7 ± 2.6, Final evaluation 10.9 ± 5.2 BFMDRS total: Baseline 78.7 ± 19.9, Final evaluation 44.7 ± 25 All comparisons were statistically significant ($p < 0.008$) Improvements were usually evident from 1 week to 2 months following surgery. Oromandibular dystonias and fixed dystonia postures changed little or did not improve by DBS. In the 3 patients with status dystonicus DBS was considered effective (although there was no improvement in BFMDRS score in one). In one patient medical therapy was withdrawn at 12 months. **Mobility** Of 5 patients who were wheelchair bound at baseline were able to walk 2–6 months after surgery	**Complications** 50% (6/12) patients suffered remote post-surgical complications. In one patient the left electrode became displaced requiring further surgery. One or both pulse generators failed in 50% (6/12) of patients.	It is useful to document all DBS non-responders to help determine appropriate case selection It is not stated whether included cases were consecutive or not and method of selection used is not described. No statistical analysis of outcomes for the 3 patients with status dystonicus was undertaken. Outcome assessment was undertaken by 3 specialists in childhood movement disorders. No details of blinding of outcome assessment.

Abbreviations used: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; PGD, primary generalised dystonia; CD, cervical dystonia; MMSE, Mini-Mental State Examination; ADL, activities of daily living; EQ-5D, Euroquol; TWSTRS – Toronto western spasmodic torticollis rating scale; SF-36 – short form health survey

Study Details	Key efficacy findings	Key safety findings	Comments
Putzke J D (2004)[2] **Case series** USA and Austria n = 52 (Essential Tremor) Patients with disabling tremor despite optical medical therapy All patients discontinued anti-tremor medication before baseline assessment. Under general anaesthesia a stimulation electrode was implanted into the ventral intermediate nucleus of the thalamus following MRI positioning. Intraoperative test stimulations were performed. Stimulation settings were adjusted for optimal tremor control. Age = 72 years, male = 58%, tremor duration = 24 years, unilateral stimulation n = 29. Follow up =19.8 months Disclosure of interest: research supported by a grant and fellowship of the Mayo Clinic.	**Motor function** Midline tremor – bilateral stimulation: Base-line (n = 45) 5.6 ± 5.1; 3 months (n = 35) 2.0 ± 2.4; p < 0.001; 24 months (n=7) 0.8 ± 0.8; p < 0.001 Midline tremor – unilateral stimulation: Base-line (n = 45) 4.1 ± 3.1; 3 months (n = 35) 1.2 ± 1.3; p < 0.001; 24 months (n=7) 1.8 ± 1.9; p N/S Activities of daily living: Base-line (n = 45) 17.8 ± 3.7; 3 months (n = 35) 6.5 ± 6.5; p < 0.001; 24 months (n=7) 6.5 ± 5.3; p < 0.001 'On' stimulation assessment of frequency and power for both contralareral resting and postural tremor showed significant improvement when compared with baseline and when compared with 'off' assessment. At 2 years follow-up the Purdue pegboard score (using both hands) was significantly improved from baseline (6.6 ± 3.2 vs 5.4 ± 2.8) (p < 0.001), although there was no significant difference at 1 or 2 months.	**Operative complications** One patient required placement of a second DBS lead 14 months after initial surgery. One case had no permanent electrode placed as no response was found during test stimulation. Eight leads required repositioning, and two leads broke during follow-up. One DBS system was explanted due to infection at 22 months follow-up. Stimulator setting adjustment was undertaken at 63% (231/367) of clinic visits **Side effects** Effect: Unilateral / Bilateral Dysarthria: 0% / 27% (6/22) Disequilibrium: 9 (2/22) / 23% (5/22) Paresthesia: 14% (3/22) / 5% (1/22) Motor disturbance: 5% (1/22) / 9% (2/22)	A consecutive sample of patients. Diagnosis was made by one neurologist for consistency Between 3 and 5% of participants did not complete all measures at each evaluation interval At each follow-up point outcomes were assessed with stimulation on and off with overnight or at least 1-hour washout period. Assessment on stimulation was undertaken before the settings were adjusted to optimise therapy, giving a conservative measure of efficacy. It is not stated whether outcome assessment is undertaken on or off medical therapy Comparison of drop-out rates found that at 2-year follow-up significantly fewer patient with unilateral then bilateral stimulation were available. Analysis also undertaken to estimate scores for drop outs using either the worst score, baseline score, or most recent score carry forward techniques.

Abbreviations used: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; PGD, primary generalised dystonia; CD, cervical dystonia; MMSE, Mini-Mental State Examination; ADL, activities of daily living; EQ-5D, Euroquol; TWSTRS – Toronto western spasmodic torticollis rating scale; SF-36 – short form health survey

Study Details	Key efficacy findings	Key safety findings	Comments
Lee J Y K (2005)[3] **Case series** USA n = 19 (Essential Tremor) Cases from May 1997 to November 2003 Patients with sever tremor causing disability refractory to medical management. DBS using the activa tremor system. Electrodes were positioned using MRI guidance to the ventralis intermedius nucleus of the thalamus, Stimulation testing under local anaesthesia, and implantation of the pulse generator with general anaesthesia. Age = 60 years, male = 63%, duration of symptoms = 23 years, upper extremities tremor n = 19, head tremor n = 9, lower extremities tremor n = 1. Follow-up =27 months Disclosure of interest: not stated	**Surgical parameters** Implantation of the DBS system was successful in 95% (18/19) of cases. In one patient temporary electrode placement eliminated tremor. This case was excluded from analysis. All patients were discharged the day following surgery. Approximately half of the patients did not require further adjustment of stimulation once initial programming was completed. **Functional assessment.** The Fahn-Tolosa-Marin action tremor score was used to evaluate outcome Baseline / Final follow-up / p Tremor score: 3.3 ± 0.5 / 0.8 ± 0.4 / < 0.005 Handwriting score: 2.8 ± 0.9 / 1.0 ± 0.6 / < 0.005 For a subgroup of patients with at least 2 years of follow-up (mean 51 months) Baseline / Final follow-up / p Tremor score: 3.3 ± 0.5 / 0.7 ± 0.5 / 0.003 Handwriting score: 2.8 ± 0.8 / 1.1 ± 0.8 / 0.003 Eight patients demonstrated better tremor control immediately postoperatively but then deteriorated with time, but they all maintained better control than baseline score.	**Complications** Event: Frequency Lead breakage: 6% (1/18) Temporary erythema (oral antibiotics): 6% (1/18) Electrode migration (requiring surgery): 6% (1.18) Mild hand tingling during stimulation: 17% (3/18)	Not stated whether this is a consecutive cohort. Although a drawing test is described in the methods, no data on this outcome is presented. Authors state that lesioning requires no permanent placement of a device so could be considered a simpler procedure. One investigator carried out all outcome assessment Concomitant medical therapy, if any, not described

Validity and generalisability of the studies

- Reported outcomes may be affected by the efficacy of concomitant pharmacotherapy.
- There is variation between studies in target nucleus used, and on bilateral or unilateral techniques, and uncertainty about relative merits of stimulation of different target nuclei.
- In relation to dystonia, some studies included patients with primary dystonia, some included patients with secondary dystonia, and some had a mixed cohort.
- Most of reviewed studies were published in the 2004 and 2005.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Dr P Bain, Dr R Gregory, Professor TZ Aziz, Professor IR Whittle, Dr DJ Burn

- Four out of five advisors considered this procedure to be established practice
- The benefits sought with this intervention are improves quality of life, with good functional outcomes and less impairment, as well as tremor suppression.
- Reported adverse events relating to this procedure are infection, haemorrhage (possibly causing hemiparesis), Hardware failure, dysarthia, speech disturbance, cerebral oedema, and death.
- Additionally, theoretical complications may include stroke, language impairment, cognitive impairment, depression and suicide, and damage from MRI scans.
- Patient selection is important, particularly in dystonia as some patients mat respond better than others.
- Most advisors noted the importance of patients being treated by a multidisciplinary team.
- The procedure requires high quality imaging for targeting the stimulation, and those undertaking the procedure need to be familiar with the stimulating equipment.
- Nine centres already carry out DBS regularly for Parkinson's disease.
- There may be concerns about the long term efficacy of the procedure as tremors may become resistant to the stimulation, and there is no follow up of patients with dystonia for 10 years.
- There may potentially be a UK trial of DBS in dystonia.
- Audit criteria should include quality of life outcomes using recognised scales, reduction in medication requirement, neuro-psychiatric adverse events, fits, death, hardware failure, and long term efficacy.

Issues for consideration by IPAC

- This is a potentially reversible procedure, unlike palidiotomy or thalamotomy.
- There is an ongoing RCT to compare DBS (treatment group) or delayed stimulation (control group) in primary generalized dystonia http://www.clinicaltrials.gov/ct/gui/show/NCT00272246

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Appendix A: Additional papers on deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) not included in summary table 2

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Binder DK, Rau GM, Starr PA. Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. Neurosurgery 2005; 56(4):722-732	Case series n=208 FU=?	A mixed study cohort of a range of movement disorders	6 symptomatic and 10 asymptomatic haematomas reported
Bittar RG, Yianni J, Wang S, Liu X, Nandi D, Joint C et al. Deep brain stimulation for generalised dystonia and spasmodic torticollis. Journal of Clinical Neuroscience 2005; 12(1):12-16.	Case series n=12 FU=2 years	Have larger case series in Table 2	At 2 years there was a 46% improvement in overall BFMDRS scores
Burkhard PR, Vingerhoets FJ, Berney A, Bogousslavsky J, Villemure JG, Ghika J. Suicide after successful deep brain stimulation for movement disorders. [Review] [10 refs]. Neurology 2004; 63(11):2170-2172	Case series n=140 FU=9 years	A mixed study cohort of a range of movement disorders	6 of 140 DBS treated patients committed suicide in 9 year follow up
Bryant JA, De Salles A, Cabatan C, Frysinger R, Behnke E, Bronstein J. The impact of thalamic stimulation on activities of daily living for essential tremor. Surgical Neurology 2003; 59(6):479-484	Case series n=16 FU=13 months	Have larger case series in Table 2	A 34% improvement in the Fahn-Tolosa-Marin tremor rating scale
Cif L, El Fertit H, Vayssiere N, Hemm S, Hardouin E, Gannau A et al. Treatment of dystonic syndromes by chronic electrical stimulation of the internal globus pallidus. Journal of Neurosurgical Sciences 2003; 47(1):52-55	Case series n=53 FU=26 months	Included in Denby (2004) study	In secondary sytonia the effect of DBS is more limited.
Halbig, T. D., Gruber, D., Kopp, U. A., Schneider, G.-H., Trottenberg, T., and Kupsch, A. Pallidal stimulation in dystonia: Effects on cognition, mood, and quality of life. Journal of Neurology, Neurosurgery & Psychiatry (12) 1716	Case series n=15 FU=6.5 months	Have larger and longer FU case series in Table 2	BFMDRS motor scores improved by between 26 and 93%.
Hooper J, Taylor R, Pentland B, Whittle IR. A prospective study of thalamic deep brain stimulation for the treatment of movement disorders in multiple sclerosis. British Journal of Neurosurgery 2002; 16(2):102-109	Case series n=15 FU=12 months	Included in Denby (2004) study	A significant reduction in severity of tremor and in hand function
Koller WC, Lyons KE, Wilkinson SB, Pahwa R. Efficacy of unilateral deep brain stimulation of the VIM nucleus of the thalamus for essential head tremor. Movement Disorders 1999; 14(5):847-850	Case series n=60 FU=12 months	Included in Denby (2004) study	A significant improvement in head tremor at all follow up points.

Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Movement Disorders 2001; 16(3):464-468	Case series n=25 FU=40 months	Included in Denby (2004) study	Tremor scores improved from baseline with DBS switched on
Lyons KE, Pahwa R, Busenbark KL, Troster AI, Wilkinson S, Koller WC. Improvements in daily functioning after deep brain stimulation of the thalamus for intractable tremor. Movement Disorders 1998; Vol. 13(4):-692.	Case series n=22 FU=11 months	Have larger case series in Table 2	A 58% improvement in tremor activities of daily living scores when stimulation on compared to off
Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK. Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. Neurology 1998; 51:1063-1069	Case series n=33 FU=3 months	A mixed study cohort some patients with Parkinson's disease	An 83% reduction in observed contralateral tremor
Pahwa R, Lyons KE, Wilkinson SB, Troster AI, Overman J, Kieltyka J et al. Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. Movement Disorders 2001; 16(1):140-143.	Non randomised controlled trial n=35 FU=27 months	Included in Denby (2004) study	No significant differences in any efficacy outcomes between DBS and thalamotomy groups.
Stein K. Deep brain stimulation for movement disorders other than Parkinsons disease. 2001. London: Bazian Ltd (Editors), Wessex Institute for Health Research and Development, University of Southampton	Systematic review 20 case series and 1 RCT FU=?	Included in Denby (2004) study	Results varied between primary studies

Appendix B: Related published NICE guidance for deep brain stimulation for tremor and dystonia (excluding Parkinson's disease)

Guidance programme	Recommendation
Interventional procedures	IPG019 Deep brain stimulation for Parkinson's disease 1.1 Current evidence on the safety and efficacy of deep brain stimulation for Parkinson's disease appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 The clinical and cost effectiveness of deep brain stimulation for Parkinson's disease is being evaluated by the PD Surg trial, which is expected to complete randomisation in 2005/6. The results of this trial are likely to provide evidence on the most appropriate use of the procedure and clinicians are encouraged to consider randomising patients in the trial (www.pdsurg.bham.ac.uk). 1.3 It is recommended that patient selection should be made with the involvement of a multidisciplinary team, and that patients should be offered the procedure only when their disease has become refractory to best medical treatment.
Technology appraisals	None applicable
Clinical guidelines	Parkinson's disease 1.5.1 STN stimulation 1.5.1.1 Bilateral subthalamic stimulation can be used in people with PD who fit the following criteria: [D] • Motor complications which are refractory to best medical treatment • Biologically fit with no clinically significant active comorbidity • Levodopa responsive • No clinically significant active mental health problems (for example, depression) or dementia.

	1.5.2 GPI stimulation 1.5.2.1 Bilateral globus pallidus stimulation can be used in people with PD who fit the following criteria: [D(GPP)] • Motor complications which are refractory to best medical treatment • Biologically fit with no clinically significant active comorbidity • Levodopa responsive • No clinically significant active mental health problems (for example, depression) or dementia 1.5.3 Comparison of different types of deep brain stimulation 1.5.3.1 With the current evidence it is not possible to specify whether or not subthalamic nucleus or globus pallidus stimulation is the preferred surgical option for people with PD. In considering the type of surgery, account should be taken of: [D(GPP)] • the clinical condition and the lifestyle of the person with PD • the views of the person with PD after being informed of the potential benefits and drawbacks of the different surgical procedures. 1.5.4 Thalamic stimulation 1.5.4.1 Thalamic deep brain stimulation can be considered as an option in people with PD who predominantly have severe disabling tremor and where STN DBS cannot be performed. [D]
Public health	None applicable

Appendix C: Literature search for deep brain stimulation for tremor and dystonia (excluding Parkinson's disease)

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

Procedure number: 319	Procedure Name: DBS for dystonia and non parkinsons tremor	
Databases	**Version searched (if applicable)**	**Date searched**
The Cochrane Library	2005 Issue 3	26/09/2005
CRD		27/09/2005
Embase	1980 to 2005 Week 39	26/09/2005
Medline	1966 to September Week 2 2005	26/09/2005
Premedline	September 23, 2005	26/09/2005
CINAHL	1982 to September Week 3 2005	26/09/2005
British Library Inside Conferences (limited to current year only)		27/09/2005
National Research Register	2005 Issue 3	27/09/2005
Controlled Trials Registry		27/09/2005

1. *movement disorders/
2. *parkinson disease/
3. 1 not 2
4. exp *dystonic disorders/
5. *essential tremor/
6. *dystonia/
7. dystoni$.tw.
8. ((nonparkins$ or non$ parkins$) adj3 (tremor$ or disorder$)).tw.
9. or/3-8
10. deep brain stimulation/
11. (deep adj2 brain$ adj2 stimul$).tw.
12. dbs-stn.tw.
13. or/10-12
14. 9 and 13
15. animal/ not human/
16. 14 not 15

For all other databases a simple search strategy using the key words in the title was employed.