NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of deep brain stimulation for refractory epilepsy

Deep brain stimulation for difficult to treat epilepsy

Epilepsy is a chronic neurological condition characterised by recurrent seizures, in which the brain's normal electrical activity becomes overactive and abnormal. During deep brain stimulation, a thin wire is implanted into the brain. The wire is attached to an electrical stimulator, which is placed under the skin of the chest. The aim is that electrical stimulation of a particular area of the brain will suppress the abnormal electrical activity associated with a seizure.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make 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 June 2011 and updated in November 2011.

Procedure name

- Deep brain stimulation for refractory epilepsy.

Specialty societies

- Society of British Neurological Surgeons
- Association of British Neurologists
- Royal College of Paediatrics and Child Health.

Description

Indications and current treatment

Drug-resistant epilepsy / epilepsy refractory to medical treatment.

Epilepsy is a neurological condition characterised by episodes of abnormal electrical activity in the brain (seizures). Many different types of epilepsy exist, depending on the presumed focus that initiates epileptic activity, whether it remains partial or becomes generalised and whether the episodes are associated with loss of consciousness. The type of epilepsy associated with greater health risks are generalised tonic–clonic (convulsive) seizures.

The main treatment for chronic epilepsy consists of anti-epileptic drugs (AEDs) taken regularly, either singly or in combination, to prevent the recurrence of seizures. In children with epilepsy, a ketogenic diet is sometimes used as an adjunctive treatment. However, a substantial proportion of all patients with epilepsy suffer from drug-resistant epilepsy, refractory to medical treatment. These patients experience frequent seizure activity and are at risk of status epilepticus and also sudden death in epilepsy (SUDEP). If medical therapy fails to control the epilepsy adequately, surgery may be considered. Surgical options include resection (such as lesionectomy, temporal lobectomy or hemispherectomy) or disconnection (for example multiple subpial transection, which involves a series of incisions to help separate the damaged part of the brain from the surrounding area, or corpus callosotomy, which is the separation of the two hemispheres of the brain). Another option is vagus nerve stimulation, in which a small generator is implanted under the skin to send electrical impulses via the vagus nerve in the neck to the brain.

What the procedure involves

Deep brain stimulation involves implanting electrodes into specific target areas of the brain. Although the mechanisms of action are not fully understood, the aim of the procedure is to reduce or suppress seizure frequency. A potential advantage of the procedure is its reversibility. It is an option for some patients with medically refractory epilepsy when resective surgery is not indicated.

Deep brain stimulation for epilepsy is performed under general or local anaesthesia. A stereotactic frame may be used. Magnetic resonance imaging (MRI) and/or computed tomography (CT) imaging are used to identify the target area of the brain (commonly, the anterior nucleus of the thalamus). Two small holes are drilled in the skull and electrodes are implanted into the target area. The electrodes are connected to an implantable neurostimulator by means of leads which are tunnelled under the skin of the neck and scalp. The neurostimulator is surgically placed into a subcutaneous pocket below the clavicle. Postoperative imaging is usually used to confirm the location of the electrodes. A handheld remote control programming unit is used to turn the

neurostimulator on or off, adjust stimulation parameters, and monitor activity. The surgical procedure is similar to deep brain stimulation for other chronic neurodegenerative conditions.

Conventionally, constant stimulation (continuous or intermittent) has been used (known as 'open-loop'). More recently, devices incorporating EEG sensors to detect abnormal electrical brain activity (seizure or pre-seizure) are under development, so that stimulation outputs are triggered or modified accordingly.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to deep brain stimulation for refractory epilepsy. Searches were conducted of the following databases, covering the period from their commencement to 29 September 2011: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection 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 were 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, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with refractory epilepsy.
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 approximately 226 patients from 1 randomised controlled trial (RCT), 2 placebo-controlled studies, 5 case series and 1 case report[1–9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on deep brain stimulation for refractory epilepsy

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

Study details

Fisher R (2010)[1]

Randomised controlled trial

USA

Recruitment period: not reported

Study population: adults with medically refractory partial seizures, including secondarily generalised seizures.

n = 109 (54 DBS vs 55 control [stimulation off])

Mean age: 36 years
Sex: 50% (54/109) female

Patient selection criteria: age 18–65 years; partial seizures including secondarily generalised seizures, at least 6 per month, but no more than 10 per day, as recorded in a 3-month daily seizure diary; at least 3 AEDs must have failed to produce adequate seizure control prior to baseline, with 1–4 AEDs used at the time of study entry. Exclusion criteria included progressive neurologic or medical diseases, nonepileptic seizures, IQ < 70, inability to take neuropsychological tests or complete seizure diaries, pregnancy. Baseline monthly median seizure frequency was 19.5.

Key efficacy findings

Number of patients analysed: **108 (54 vs 54)**

Unadjusted median percentage change in seizure frequency from baseline

	DBS	Control
1 month post-implantation (no active stimulation)	-21.3%	-22.2%
Month 1–2	-33.9%	-25.3%
Month 2–3	-42.1%	-28.7%
Month 3–4	-40.4%	-14.5%

GEE model adjusted mean percentage difference in seizure frequency

	Adjusted % difference	p value
Per protocol (54 DBS vs 54 control)		
Month 1–2	20%	0.50
Month 2–3	-10%	0.40
Month 3–4	-29%	0.002
With outlier excluded* (53 DBS vs 54 control)		
Month 1–2	-10%	0.37
Month 2–3	-11%	0.34
Month 3–4	-29%	0.002
Intent-to-treat (54 DBS vs 55 control)		
Month 1–2	19%	0.52
Month 2–3	-10%	0.40
Month 3–4	-29%	0.002
Intent-to-treat with outlier excluded* (53 DBS vs 55 control)		
Month 1–2	-11%	0.34
Month 2–3	-11%	0.34
Month 3–4	-29%	0.002

*One patient had 210 brief partial seizures in the 3 days after initial activation. The stimulator was turned off and the new seizures stopped. Stimulation was later restored with voltage reduced to 4 V.

Key safety findings

Adverse events
808 adverse events were reported in 109 patients between implantation and 13-month follow-up; 238 were considered to be device-related.

Adverse events during the blinded phase:

	DBS	control	p
Depression	14.8% (8/54)	1.8% (1/55)	0.016
Memory impairment	13.0% (7/54)	1.8% (1/55)	0.032
Confusional state	7.4% (4/54)	0% (0/55)	0.057
Anxiety	9.3% (5/54)	1.8% (1/55)	0.113
Paraesthesia	9.3% (5/54)	3.6% (2/55)	0.271
Partial seizures with secondary generalisation*	9.3% (5/54)	5.5% (3/55)	0.489
Simple partial seizures*	5.6% (3/54)	1.8% (1/55)	0.363
Complex partial seizures*	9.3% (5/54)	7.3% (4/55)	0.742
Anticonvulsant toxicity	5.6% (3/54)	7.3% (4/55)	1.00
Dizziness	5.6% (3/54)	7.3% (4/55)	1.00
Headache	3.7% (2/54)	5.5% (3/55)	1.00

*new or worse seizures, or seizures meeting serious adverse event criteria.

Depression symptoms resolved in 4 of the 8 patients in the DBS group over an average of 76 days (7 of the 8 patients had a prior history of depression and 3 were on antidepressant

Comments

Follow-up issues:
- One control group patient had only 66 of 70 protocol-required diary days for the primary analysis and was excluded.
- An additional patient underwent electrode implantation but was not randomised.

Study design issues:
- Prospective, randomised, double-blind, parallel group design.
- Primary efficacy outcome was reduction in monthly seizure rate from baseline.
- All patients had DBS electrodes implanted.
- One month after implantation, patients were randomised to stimulation at 5 V or no stimulation at 0 V (controls).
- Randomisation was done by a central statistical site, using random numbers tables.
- No care or assessment personnel knew the voltage settings.
- After 3 months of blinded treatment, all patients received stimulation from month

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

Study details	Key efficacy findings	Key safety findings	Comments
Technique: implantation was with Medtronic DBS leads. Electrodes were implanted in the anterior nucleus of the thalamus bilaterally using a stereotactic technique. Stimulation was initially set at 5 V, using 90 micro second pulses, 145 pulses/second, 1 minute on and 5 minutes off. **Mean follow-up: not reported (mean duration of active stimulation = 3 years)** Conflict of interest/source of funding: the study was supported by Medtronic Inc.	**Improvement in complex partial seizures during blinded phase (outlier removed):** • DBS = 36.3% • Control = 12.1%, p = 0.04 **Injuries produced by seizures during blinded phase:** • DBS = 7% • Control = 26%, p = 0.01 **Median seizure reduction in patients with seizure origin in 1 or both temporal regions:** • DBS = 44.2% (n = 33) • Control = 21.8% (n = 29), p = 0.025 There were no significant differences in seizure reduction for patients with seizure origin in frontal, parietal, or occipital regions. ***Unblinded phase and long-term follow-up*** **Median seizure frequency percentage change from baseline:** • 13 months = -41% (n = 99) • 25 months = -56% (n = 81) **Median seizure frequency percentage change from baseline (intent-to-treat):** • 13 months = -44% (n = 108) • 25 months = -57% (n = 103) **50% responder rate:** • 13 months = 43% (n = 99) • 25 months = 54% (n = 81) • 37 months = 67% (n = 42) **Liverpool Seizure Severity Scale change from baseline (lower is better):** • 13 months = -13.4 ± 21.4 (n = 103), p < 0.001 • 25 months = -12.4 ± 20.7 (n = 99), p < 0.001 **Quality of Life in Epilepsy score change from baseline (higher is better):** • 13 months = 5.0± 9.2 (n = 102), p < 0.001 • 25 months = 4.8 ± 9.3 (n = 98), p < 0.001 14 patients were seizure free for at least 6 months, 8 for at least 1 year, 4 for at least 2 years and 1 for over 4 years.	medication at baseline). All memory impairments resolved over 12–476 days. Neuropsychological test scores for cognition and mood did not differ between the groups at the end of the blinded phase. **Adverse events during entire study period** *Deaths* There were 5 deaths during a mean follow-up of 3 years (none were during the blinded phase). 1 patient died before implantation due to probable SUDEP. In the long-term follow-up phase, 1 patient drowned and another committed suicide. One patient each in the unblinded and long-term follow-up phase died from SUDEP. None of the deaths were judged to be device-related. *Haemorrhage* 5 asymptomatic haemorrhages were detected incidentally by neuroimaging (study arm not reported). *Infection* 13% (14/109) of patients developed implant site infections either in the stimulator pocket, the tunnelled lead extension tract or at the site of the burr hole (study arm not reported). Another patient had a meningeal reaction. All infections were treated with antibiotics, and 9 with additional removal of hardware. 3 patients later had reimplantation. *Status epilepticus* 4.5% (5/109) of patients had status epilepticus (3 were in the stimulated group during the blinded phase and 2 were after the blinded phase). 2 were before initiation of stimulation (in patients who had missed 1 or more doses of their AEDs), 1 was during month 2 of the	4 to month 13 in an unblinded phase. • Medications were kept constant during the 3-month blinded phase and the 9-month unblinded phase. • At the end of month 13, AEDs and stimulation parameters could vary freely. • A sample size of 102 provided 80% power to detect a 25% larger seizure reduction in the stimulated group. • Analysis was done using a protocol-prespecified GEE model for repeated measures. The prespecified factors included the intercept, treatment effect, log of the baseline seizure counts, baseline covariates, visit and treatment-by-visit interaction. **Study population issues**: • The 2 groups were comparable with regard to demographic and seizure history characteristics. • 49 patients had previously been treated by vagus nerve stimulation and 27 patients had a history of previous epilepsy surgery.

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
		blinded phase, 1 occurred when the stimulator was turned on after the blinded phase and 1 occurred at month 49, 1 year after stimulation was discontinued.	

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

Study details	Key efficacy findings	Key safety findings	Comments
Boon P (2007)[2] **Case series** Belgium Recruitment period: not reported Study population: patients with refractory medial temporal lobe epilepsy **n = 12** Age: NR, Sex: NR Patient selection criteria: inclusion criteria were suspicion of temporal lobe epilepsy on the basis of video-EEG monitoring; seizure frequency of at least 1 complex partial seizure per month; requirement for invasive video-EEG monitoring in the bilateral medial temporal lobe area and other subdural brain areas. Technique: two electrodes (Medtronic) were implanted in each hemisphere (in the amygdala and hippocampus) and high frequency stimulation was used. Initial DBS was done using a temporary external pulse generator during a trial period before implanting patients with an internalised pulse generator. During the acute stimulation period, continuous stimulation was delivered.	Number of patients analysed: **12** Out of 12 patients, 1 decided on resection before the test phase started. In 1 patient, the stimulator seemed not to work during the test phase, so rather than implantation they had resection surgery. In 10 it seemed to work well and showed promise so they were implanted and entered into the DBS study. **Mean monthly seizure frequency during the last 6 months of follow-up compared with preintervention baseline period:** • Seizure free (for ≥12 months) = 10% (1/10) • >90% reduction = 10% (1/10) • ≥50% reduction = 50% (5/10) • 30–49% reduction = 20% (2/10) • <30% reduction = 10% (1/10) (considered to be a nonresponder) Both patients who underwent resective surgery were seizure free for ≥12 months.	**Complications** • Asymptomatic haemorrhage = 8.3% (1/12) (diagnosed on routine MRI scan). Surgical implantation of the generator and perioperative course were uneventful in all patients. None of the patients showed changes in bedside neurological and neuropsychological testing.	**Study design issues**: • DBS was performed using the electrodes implanted for diagnostic reasons. • There was a 6-month pre-intervention baseline period. • After 48 hours of video-EEG monitoring, AEDs were gradually tapered until habitual seizures were recorded. Stimulation was then performed with the aim of keeping patients on the tapered regimen. • The criterion for implantation of a pulse generator and entering the chronic stimulation phase was a reduction of interictal spikes in the stimulated area of >50% during 7 consecutive days in the acute stimulation phase compared with the AED-tapered phase.

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Mean follow-up: 31 months Conflict of interest/source of funding: implanted devices were provided by Medtronic Europe.			

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Velasco AL (2007)[3]

Placebo-controlled study (randomised phase for 1 month followed by open phase)

Mexico

Recruitment period: not reported

Study population: patients with refractory temporal lobe epilepsy

n = 9 (4 stimulation ‘on’ vs 5 stimulation ‘off’ for first month)

Mean age: 29 years (range 14–43)
Sex: 33% (3/9) female

Patient selection criteria: patients with intractable temporal lobe epilepsy due to undergo bilateral hippocampal electrode implantation for diagnostic purposes.

Technique: DBS electrodes (Medtronic) were implanted in the hippocampus. Stimulation parameters: cyclic stimulation with 1-minute trains of square pulses with a 4 minute interstimulus interval. Trains consisted of a 130 Hz frequency with individual pulses of 450 micro second in duration and amplitude of 300 micro amps.
Mean follow-up: 37 months
Conflict of interest/source of funding: none reported.</td>
<td>Number of patients analysed: 9

Seizure count per month during baseline, ‘off’ period, and 18 months of electrical stimulation
<table>
<tr><td></td><td colspan="3">Seizures/month</td></tr>
<tr><td>Patient number</td><td>Baseline</td><td>1 month ’off’</td><td>18-month follow-up</td></tr>
<tr><td>1</td><td>39</td><td>NA*</td><td>0</td></tr>
<tr><td>2</td><td>39</td><td>NA*</td><td>6</td></tr>
<tr><td>3</td><td>49</td><td>48</td><td>0</td></tr>
<tr><td>4</td><td>70</td><td>NA*</td><td>23</td></tr>
<tr><td>5</td><td>23</td><td>21</td><td>11</td></tr>
<tr><td>6</td><td>50</td><td>NA*</td><td>0</td></tr>
<tr><td>7</td><td>31</td><td>32</td><td>0</td></tr>
<tr><td>8</td><td>25</td><td>45</td><td>9</td></tr>
<tr><td>9</td><td>15</td><td>15</td><td>1</td></tr>
</table>
*stimulation set to ’on’.

There were 2 types of responder to stimulation. 5 patients had an evident drop in seizure count within the first or second month of DBS. Four of these became seizure free and 1 had brief, occasional complex partial seizures with no generalisation. The remaining 4 patients showed a slower response, which appeared 6–8 months after stimulation. None of these 4 patients became seizure free. The only consistent difference between the groups was that good responders had normal MRI whereas poor responders had hippocampal sclerosis identified on MRI.

For the entire patient group, there was a significant reduction in seizures from month 2 of stimulation, becoming highly significant progressively from month 6 on ($p < 0.0005$).

In 5 patients with normal MRI, there was a significant reduction from month 1, becoming highly significant from month 3 on ($p < 0.0005$).

In 4 patients with hippocampal sclerosis, there was a reduction in seizure frequency that became significant at month 8 ($p < 0.05$).</td>
<td>Postsurgical control MRIs showed no evidence of haemorrhage or oedema.

• Skin erosion and local infection after 24 months in 3 out of 9 patients (1 patient required hospitalisation for intravenous antibiotics and plastic surgery to correct the problem and 3 months later required explantation due to skin erosion and infection at several electrode and lead points; 2 patients required explantation after 24 months).

No patient had neuropsychological deterioration.</td>
<td>Study design issues:
• Patients had been followed up for at least 6 months prior to diagnostic implantation.
• Randomisation was done by lottery numbers; half the patients had an initial 1 month ‘off’ period and the other started stimulation immediately after the DBS system was implanted.
• Patients were unaware of device activation.
• After defining the epileptic focus, the diagnostic electrodes were removed and permanent electrodes were implanted.

Other issues:
• The authors noted that use of an old model of extension cable with a larger diameter connector may have accounted for 2 cases of skin erosion.
• The authors noted that 1 month is not sufficient time for patients with hippocampal sclerosis to show a response.</td>
</tr>
</table>

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

Study details	Key efficacy findings	Key safety findings	Comments
Fisher RS (1992)[4] **Placebo-controlled cross-over study** USA Recruitment period: not reported Study population: patients with intractable epilepsy. **n = 7 (stimulation 'on' or 'off' in 3-month blocks)** Age range: 16–41 years Sex: 57% (4/7) female Patient selection criteria: patients with intractable epilepsy. 1 patient had partial complex seizures only but had frequent falls and injuries. All other patients had primary or secondarily generalised tonic–clonic seizures. Technique: DBS electrodes were implanted in the CM bilaterally. Stimulation parameters: 90-mus pulses at 65 pulses/second, 1 minute of each 5 minutes for 2 hours/day with voltage set to half the sensory threshold. **Mean follow-up: NR** Conflict of interest/source of funding: study was supported by Medtronic Inc.	Number of patients analysed: **7** During the stimulator-on period, 4 of the 6 patients with tonic–clonic seizures improved with respect to baseline, 1 worsened and 1 stayed the same. During stimulator-off period, 4 patients improved, 1 worsened and 1 could not be analysed because stimulation was left on. **Mean reduction of tonic–clonic frequency with respect to baseline:** • Stimulation on = 30% • Stimulation off = 8% (p = not significant). **Mean seizure frequency per month (excluding 1 patient who showed the greatest benefit but who had no stimulator-off period)**: • Baseline = 28.4 ± 8.2 • Stimulator-off period = 21 ± 9.2 • Washout period = 29.3 ± 30.2 • Stimulator-on period = 24.4 ± 23.8 (p = not significant) In open-label follow-up period with stimulator trains continuing for 24 hours/day, 3 of 6 patients reported at least a 50% decrease in seizure frequency. No patient experienced complete remission.	1 patient had a 'minimal' haemorrhage in the vicinity of a depth electrode site, detected by postimplantation CT scan. The patient had no clinical symptoms and recovered uneventfully. 1 patient required repair of the connection to the pulse generator. There were no significant differences in any of the cognitive assessment tests performed. No patient experienced emergence of new seizure types.	**Study design issues**: • Cross-over design – stimulation was set to 'on' or 'off' in 3-month blocks with a 3-month washout period. • 9-month double-blind study was followed by open label follow-up period, during which the stimulator was known to be on.

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Andrade DM (2006)[5]

Case series

Canada

Recruitment period: NR

Study population: patients with epilepsy not responsive to treatment with multiple AEDs

n = 8

Age range: 18–45 years
Sex: NR

Patient selection criteria: frequent and disabling seizures not responsive to multiple AEDs; not candidates for resective surgical treatment; no lateralising structural abnormalities on brain MRI.

Technique: Medtronic DBS electrodes were implanted in the centromedian nucleus in 2 patients. The remaining patients were implanted with anterior nucleus electrodes. Activation and programming of the stimulators usually started 1 month after the electrodes were implanted. Stimulation parameters varies (frequency from 100 to 185 Hz, voltage 1–10 V, pulse duration 90 to 120 micro seconds, continuous vs cycling.

Mean follow-up: 5 years</td>
<td>Number of patients analysed: 8

Seizure frequency by patient at baseline, prestimulation, during ‘off’ period and during long-term follow-up
<table>
<tr><td></td><td colspan="4">Patient</td></tr>
<tr><td></td><td>AN1</td><td>AN2</td><td>AN3</td><td>AN4</td></tr>
<tr><td>Baseline</td><td>10.5</td><td>15.0</td><td>125</td><td>120</td></tr>
<tr><td>Prestimulation</td><td>7.0</td><td>11.0</td><td>65.0</td><td>11.0</td></tr>
<tr><td>‘Off’ period</td><td>6.5</td><td>14.0</td><td>61.7</td><td>12.5</td></tr>
<tr><td>1 year</td><td>7.45*</td><td>11.7</td><td>60.0*</td><td>11.6*</td></tr>
<tr><td>2 years</td><td>7.5</td><td>14.9</td><td>NR</td><td>15.9*</td></tr>
<tr><td>3 years</td><td>6.4*, **</td><td>11.8</td><td>NR</td><td>21.1*</td></tr>
<tr><td>4 years</td><td>NR</td><td>10.5</td><td>45.7*</td><td>25.3*</td></tr>
<tr><td>5 years</td><td>1.0**</td><td>9.9</td><td>NR</td><td>26.4</td></tr>
<tr><td>6 years</td><td>NR</td><td>4.7*</td><td>NR</td><td>NR</td></tr>
<tr><td>7 years</td><td>NR</td><td>5.7*</td><td>NR</td><td>NR</td></tr>
</table>
* p < 0.05
**numbers denote stimulation ‘off’ period during follow-up
<table>
<tr><td></td><td colspan="4">Patient</td></tr>
<tr><td></td><td>AN5</td><td>AN6</td><td>CM1</td><td>CM2</td></tr>
<tr><td>Baseline</td><td>60.0</td><td>3.7</td><td>64.5</td><td>9.5</td></tr>
<tr><td>Prestimulation</td><td>11.0</td><td>2.0</td><td>61.0</td><td>8.0</td></tr>
<tr><td>‘Off’ period</td><td>23.0</td><td>2.8</td><td>52.5*</td><td>15.1*</td></tr>
<tr><td>1 year</td><td>16.4*</td><td>3.6</td><td>80.6</td><td>12.9</td></tr>
<tr><td>2 years</td><td>13.0*</td><td>2.8</td><td>90.0*</td><td>15.1*</td></tr>
<tr><td>3 years</td><td>8.3*</td><td>5.2</td><td>67.9</td><td>NR</td></tr>
<tr><td>4 years</td><td>9.2*</td><td>3.8</td><td>53.3*</td><td>NR</td></tr>
<tr><td>5 years</td><td>5.1</td><td>NR</td><td>53.0*</td><td>NR</td></tr>
<tr><td>6 years</td><td>NR</td><td>NR</td><td>44.1*</td><td>NR</td></tr>
<tr><td>7 years</td><td>NR</td><td>NR</td><td>77.8</td><td>NR</td></tr>
</table>
* p < 0.05

Implantation of the DBS electrodes was followed by seizure reduction in all patients.

Patient AN2 had further adjuvant AEDs in year 5 and patient AN1 had new adjuvant AEDs prior to the significant reduction in seizure frequency seen in year 5.</td>
<td>Complications

One patient had intermittent nystagmus during chronic stimulation phase (cycling stimulation).

One patient had possible auditory hallucinations and anorexia during a 6-week period of continuous stimulation at 185 Hz.

One patient had lethargy during a 4-day period of continuous stimulation.</td>
<td>Study design issues:
• The first 5 anterior nucleus patients underwent a 2-month, single-blind period of stimulation ‘off’.
• No changes were made in AEDs for at least the first 2 years post-implantation.

Study population issues:
• 3 patients had symptomatic generalised epilepsy with tonic–clonic seizures and the rest had multifocal/partial epilepsy with secondarily generalised seizures.

Other issues:
• Some patients had multiple changes in their AEDs after 2 years post-implantation.
• The authors noted the possibility that the beneficial response in seizure control could be primarily related to the microthalamotomy caused by electrode insertion.
• There is the possibility of a significant placebo effect.</td>
</tr>
</table>

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Conflict of interest/source of funding: 2 authors are consultants for Medtronic Inc.			

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Velasco AL (2006)[6]

Case series

Mexico

Recruitment period: NR

Study population: patients with Lennox-Gastaut syndrome (severe form of childhood epilepsy)

n = 13

Age range: 4–22 years
Sex: NR

Patient selection criteria: patients with Lennox-Gastaut syndrome (all had generalised tonic–clonic seizures and atypical absences).

Technique: Medtronic DBS electrodes were implanted into the CM. Stimulation parameters: 130 Hz, 0.45 ms, 400–600 micro amps (alternating 1-minute stimulation on each side with a 4-minute interval between right and left sides).

Mean follow-up: 46 months (range 23–132)

Conflict of interest/source of funding: NR</td>
<td>Number of patients analysed: 13

After 6 months of DBS, all patients had a stable seizure reduction throughout the 18-month follow-up period.

Overall seizure reduction = 80%

Significance in total seizure reduction from baseline to the 18-month follow-up was <0.0001.

Non-convulsive and convulsive, recurrent, epileptic-status episodes that occurred more than once per year in 3 patients did not recur during the 18- to 54-month follow-up period.

Improvement of ability scales after 18 months of DBS
(0 = totally disabled, 1 = partially dependent, 2 = partially independent, 3 = independent, 4 = able to attend a regular school supported by special education to improve performance)
<table>
<tr><th>Patient</th><th>Ability scale before DBS</th><th>Ability scale after DBS</th></tr>
<tr><td>1</td><td>0</td><td>4</td></tr>
<tr><td>2</td><td>0</td><td>4</td></tr>
<tr><td>3</td><td>1</td><td>3</td></tr>
<tr><td>4</td><td>0</td><td>3</td></tr>
<tr><td>5</td><td>0</td><td>2</td></tr>
<tr><td>6</td><td>0</td><td>3</td></tr>
<tr><td>7</td><td>0</td><td>3</td></tr>
<tr><td>8</td><td>0</td><td>3</td></tr>
<tr><td>9</td><td>1</td><td>2</td></tr>
<tr><td>10</td><td>0</td><td>2</td></tr>
<tr><td>11</td><td>1</td><td>1</td></tr>
<tr><td>12</td><td>2</td><td>2</td></tr>
<tr><td>13</td><td>1</td><td>1</td></tr>
</table>
$p < 0.04$ for whole group.

Improvement in seizure number was concordant with ability scale scores (the 2 patients with ability score of 4 became seizure free).

After initial 18-month period, DBS was discontinued temporarily or permanently in 4 patients (1 because the batteries were depleted,</td>
<td>No patient had evidence of postsurgical haemorrhage or oedema (assessed by MRI).

2 patients had explantation at months 20 and 54 because of repeated and multiple skin erosions that could not be controlled by plastic surgery procedures.</td>
<td>There may be some patient overlap with Velasco F, 2002.

Follow-up issues:
• Patients were followed up every 3 months for an EEG, to check the stimulation system and to return the seizure diary. After 18 months, patients returned once a year.

Study design issues:
• Baseline period consisted of a 6-month follow-up before implantation. During this time, the patient's relatives were trained to keep a seizure diary.

Study population issues:
• 7 patients had normal and 6 had abnormal MRI scans.
• Patients demonstrated severe baseline cognitive impairment.</td>
</tr>
</table>

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

Study details	Key efficacy findings	Key safety findings	Comments
	2 were explanted because of skin erosions and 1 patient had 2 accidents related to seizure occurrence that resulted in rupture of electrode lead and connector cable and fracture of DBS extracranial portion). With 1 exception, all patients who discontinued stimulation experienced an increase in seizures. Seizure numbers during 3- to 5-month 'off' periods were significantly lower than for the baseline period ($p = 0.02$).		

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

Study details	Key efficacy findings	Key safety findings	Comments
Graves NM (2005)[7] **Case series** Recruitment period: NR Study population: patients with intractable epilepsy. **n = 17** Age range: 19–47 years Sex: 50% (7/14) female (data for 3 patients were not available) Patient selection criteria: medically intractable epilepsy (including simple partial, complex partial and generalised tonic–clonic). Technique: Medtronic DBS electrodes were implanted bilaterally into the anterior nucleus. Intermittent high-frequency stimulation was used. **Mean follow-up: 12 months** Conflict of interest/source of funding: NR	Number of patients analysed: **14** **Median reduction in total seizure frequency:** • **3-month follow-up = 63.8%** • **6-month follow-up = 63.3%** • **12-month follow-up = 58.6%** 57.1% (8/14) of patients experienced a ≥50% reduction in seizure frequency at 3- and 6-month follow-up). Responder rate at 12 months = 66.7% (defined as a patient with 50% or greater decrease in seizure frequency). In subgroup of patients with seizures involving the temporal and/or frontal lobes, median percent change in frequency at 3 months = -78.8% (n = 9). In this subgroup, 77.8% were responders. No patient became seizure-free for the full duration of follow-up, but several patients had elimination of seizures of the type leading to falls. None of the patients could determine whether the stimulation was on or off at the parameters used for treatment.	Of the 3 patients not included in main analysis, 1 experienced a subdural haemorrhage during the DBS implantation procedure and later had an intracerebral haemorrhage leading to increased intracranial pressure. The patient underwent an evacuation of the subdural haemorrhage and a right frontal resection. The patient was hemiparetic and obtunded at 1-week after the event. 92.9% (13/14) patients experienced related adverse events, none judged to be serious. • Lead fracture leading to device explant = 7.0% (1/14) • Minor pain at site of device component = 28.6% (4/14) • Non-painful tingling = 21.4% (3/14) • Head laceration = 7.0% (1/14) • Depression = 14.3% (2/14) • Increased irritability = 14.3% (2/14)	**Study design issues**: • Raw data were not available for 3 patients. These patients were not included in the analysis.

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

Study details	Key efficacy findings	Key safety findings	Comments
Velasco F (2002)[8] **Case series** Mexico Recruitment period: NR Study population: patients with difficult to control seizures and non-candidates for ablation of the epileptic focus **n = 49** Age: NR; Sex: NR Patient selection criteria: patients with severe seizures uncontrolled by adequate doses of AEDs; patients were not candidates for surgical resection because of the location of the epileptic foci or the presence of bilateral or multiple foci. Technique: electrodes were implanted into the CN. Stimulation parameters: 60–130 Hz, 0.21–0.45 ms, 400–600 micro amps; alternating 1-minute stimulation with interval of 4 minutes between right and left sides. **Follow-up: 1–9 years** Conflict of interest/source of funding: NR	Number of patients analysed: **49** **Group 1 (n = 5):** Focal motor seizures with frequent generalisation in the form of adversive tonic seizures and generalised tonic–clonic convulsions (children aged 3–7 years) During the first month, there was a significant decrease ($p < 0.01$) in the occurrence of secondary generalised tonic–clonic and tonic and adversive motor seizures. By the end of 3 months, 4 out of 5 patients were seizure free. The remaining patient had seizure control after 4 months and remained so for 8 months when the stimulation system had to be explanted. **Group 2 (n = 16):** Partial complex seizures with frequent generalisation Complex partial seizures were not significantly reduced during the first year of DBS although longer follow-up periods showed partial improvement. However, most patients were satisfied because secondary generalised tonic–clonic convulsions significantly decreased or disappeared ($p < 0.01$). **Group 3 (n = 6):** tonic seizures with fencing posture, frequently associated with atypical absences and generalised tonic–clonic convulsions. Tonic seizures were significantly decreased ($p < 0.001$) as were secondary tonic–clonic convulsions. No patients in this group were seizure free. **Group 4 (n = 22):** Lennox-Gastaut syndrome (atypical absences and generalised tonic–clonic convulsions) Seizures and paroxysmal discharges were significantly decreased ($p < 0.001$). 3 out of 22 patients became seizure free.	The DBS system was explanted in 1 patient because of multiple skin erosions.	There may be some patient overlap with Velasco AL, 2006.

Abbreviations used: AED, anti-epileptic drug; AN, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; EEG, electroencephalography; GEE, generalised estimating equations; NA, not applicable; NR, not reported; SUDEP, sudden unexplained death in epilepsy.

Study details	Key efficacy findings	Key safety findings	Comments
Miller PM (2009)[9] **Case report** Study population: patients with epilepsy implanted with DBS electrodes, with wire tethering of DBS extension wire. **n = 2** Age: 23 and 40 years Sex: both female Technique: simultaneous bilateral stimulation of the anterior nucleus of the thalamus. Conflict of interest/source of funding: NR	**Patients with moderate to severe wire tethering or 'bowstringing' of DBS extension wire** Both patients presented with complaint of tightness, discomfort, prominence or limitation of motion related to implantation of DBS system. Patient 1: Wire tethering occurred 12 months after implantation. The patient had a history of infection requiring removal of the extension wires and pulse generator with subsequent reimplantation. The patient opted for non-surgical management and the condition has persisted unabated. Patient 2: wire tethering occurred 8 months after implantation. Complicating factors were possible drainage and exuberant scarring at the pulse generator site. The patient underwent removal of all hardware, mostly due to suboptimal response. No follow-up is available.		The authors noted that none of the other 12 patients with epilepsy treated at the centre developed this complication.

Efficacy

Seizure frequency

An RCT of 109 patients who had DBS electrodes implanted in the anterior nucleus of the thalamus reported a 29% greater reduction in seizures for 54 patients with stimulation 'on' compared with 55 patients with stimulation 'off' (control) at the end of a 3-month blinded phase ($p = 0.002$)[1]. Unadjusted reductions in seizure frequency were 15% in the control group and 40% in the stimulated group. After the blinded phase, all patients received stimulation and there was a 56% median reduction in seizure frequency at 2-year follow-up (n = 81). In total, 14 patients were seizure free for at least 6 months, 8 for at least 1 year, 4 for at least 2 years and 1 for over 4 years.

In a case series of 12 patients, of whom 10 had a generator implanted for long-term stimulation, 90% (9/10) of patients responded to DBS with a reduction in mean monthly seizure frequency of at least 30%[2].

In a case series of 9 patients, there was a significant reduction in seizures from month 2 of stimulation, becoming highly significant from month 6 ($p < 0.0005$)[3].

In a case series of 8 patients, 5 had a 50% or more seizure reduction over a mean follow-up period of 5 years, although the reduction was preceded by changes in AEDs in 2 patients. Implantation of the DBS electrodes was followed by a seizure reduction in all patients before stimulation was started[5].

In a case series of 13 patients, there was an overall seizure reduction of 80% from baseline to the 18-month follow-up ($p < 0.0001$)[6].

In a case series of 17 patients, describing efficacy data for 14 patients, there was a median seizure reduction of 59% at 12-month follow-up[7].

Quality of life

The RCT of 109 patients reported that the Quality of Life in Epilepsy score was statistically significantly improved after 13 and 25 months follow-up (n = 102 and 98, respectively; $p < 0.001$; all patients received stimulation after an initial 3-month blinded phase)[1].

In the case series of 13 patients, 10 had improvements in their ability scale score after 18 months of DBS ($p < 0.04$ for the whole group); 2 patients became seizure-free[6].

Safety

Haemorrhage

The case series of 17 patients reported 1 case of subdural haemorrhage during the DBS implantation procedure. The patient later had an intracerebral haemorrhage leading to increased intracranial pressure. Evacuation of the subdural haemorrhage and a right frontal resection were performed; the patient was hemiparetic and obtunded at 1-week after the event[7].

The RCT of 109 patients implanted with DBS electrodes reported that 5% (5/109) of patients had asymptomatic haemorrhages detected incidentally by neuroimaging[1].

The case series of 12 patients reported 1 case of asymptomatic haemorrhage diagnosed on a routine MRI scan[2].

Skin erosions/infection

The RCT of 109 patients implanted with DBS electrodes reported that 13% (14/109) of patients developed implant site infections, either in the stimulator pocket, the tunnelled lead extension tract or at the site of the burr hole. Another patient had a meningeal reaction. All infections were treated with antibiotics, and 9 patients had additional removal of hardware; 3 patients later had reimplantation[1].

A case series reported that 33% (3/9) of patients had skin erosion and local infection 24 months after implantation; all required explantation. One patient was hospitalised for intravenous antibiotics and plastic surgery to correct the problem, and 3 months later required explantation due to skin erosion and infection at several electrode and lead points[3].

The case series of 13 patients reported that 2 patients had explantation (at 20 months and 54 months) because of repeated and multiple skin erosions that could not be controlled by plastic surgery procedures[6].

Depression/memory impairment

The RCT of 109 patients reported depression in 15% (8/54) of patients treated by DBS (stimulation ‘on’) compared with 2% (1/55) of control patients (stimulation ‘off’) during the blinded phase ($p = 0.016$)[1]. Depression symptoms resolved in 4 of the 8 DBS patients within an average of 76 days (3 patients were on medication for depression at baseline). Memory impairment was reported in 13% (7/54) of patients in the DBS group and 2% (1/55) of patients in the control group ($p = 0.032$). No memory impairment was judged to be serious and all resolved over 12–476 days.

Status epilepticus

The RCT of 109 patients reported 5% (5/109) of patients had status epilepticus (3 were in the stimulated group during the blinded phase and 2 were after the blinded phase); 2 were identified before initiation of stimulation (in patients who

had missed 1 or more doses of their AEDs), 1 was during month 2 of the blinded phase, 1 occurred when the stimulator was turned on after the blinded phase and 1 occurred at month 49, 1 year after stimulation was discontinued[1].

Other

The RCT of 109 patients reported a total of 5 deaths during a mean follow-up of 3 years; 1 patient died before implantation of electrodes because of probable SUDEP, 2 further patients died from SUDEP (1 in the unblinded phase and the other during the long-term follow-up), 1 patient drowned during the long-term follow-up phase and another committed suicide. None of the deaths were judged to be device-related[1].

A case report described 2 patients with moderate to severe wire tethering of the DBS extension wire, 8 and 12 months after implantation respectively[9]. One patient opted for non-surgical management and the condition persisted unabated; the other patient had the DBS system removed.

The case series of 8 patients reported 1 case each of intermittent nystagmus; possible auditory hallucinations and anorexia; and lethargy[5].

Validity and generalisability of the studies

- The patient populations were heterogeneous and included patients with different types of epilepsy and seizures (simple partial, complex partial and generalised tonic–clonic seizures), both between and within studies. The RCT included patients with medically refractory partial seizures, including secondarily generalised seizures[1].
- Different studies involved stimulation of different parts of the brain. The RCT and 1 case series involved bilateral implantation of electrodes into the anterior nucleus of the thalamus[1,7]. Four studies involved implantation of electrodes into the centromedian thalamic nucleus[4,5,6,8]. Two further studies involved implanting electrodes into the hippocampus (one also implanted electrodes into the amygdala)[2,3].
- The type of stimulation and parameters used varied between studies. Five studies used cyclic stimulation[1,4,5,7,8], 1 study used continuous stimulation[2] and 1 study used a combination of the two[6].
- There may be a lesional effect of electrode placement in addition to the effect of stimulation. In 1 study, implantation of the electrodes was followed by a reduction in seizure rate prior to activation of the pulse generators[6].
- The RCT stated that patients were unaware of their treatment group, so the difference was not caused by a placebo effect. However, there is likely to be a placebo effect associated with this procedure, which may be evident during open-label trials. A case series of 17 patients reported that none of them knew whether stimulation was on or off[7].
- In at least 1 study, changes in AEDs during the follow-up period may have contributed to the observed reduction in seizure frequency[5].

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

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

Interventional procedures

- Vagus nerve stimulation for refractory epilepsy in children. NICE interventional procedures guidance 50 (2004). Available from www.nice.org.uk/guidance/IPG50
- Deep brain stimulation for refractory chronic pain syndromes (excluding headache). NICE interventional procedures guidance 382 (2011). Available from www.nice.org.uk/guidance/IPG382
- Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedures guidance 381 (2011). Available from www.nice.org.uk/guidance/IPG381
- Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). NICE interventional procedures guidance 188 (2006). Available from www.nice.org.uk/guidance/IPG188
- Deep brain stimulation for Parkinson's disease. NICE interventional procedures guidance 19 (2003). Available from www.nice.org.uk/guidance/IPG19

Clinical guidelines

- Epilepsy in adults and children. NICE clinical guideline 20 (2004). Available from www.nice.org.uk/guidance/CG20

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Professor S Eljamel, Mr A Green, Mr A Jenkins (Society of British Neurological Surgeons) Mr J Ross (Royal College of Paediatrics and Child Health).

- One Specialist Adviser performs DBS regularly but is yet to perform it for epilepsy and 2 Advisers reported that they have never performed it.

- Three Specialist Advisers described the procedure as a minor variation on an existing procedure. One Specialist Adviser described the procedure as definitely novel and of uncertain safety and efficacy.
- Adverse events (reported in the literature or theoretical) include death, stroke, infection, haematoma, and breakage and displacement of leads.
- Key efficacy outcomes included reduction in seizure frequency and medication use, and improvement in quality of life.
- An established DBS service and an epilepsy MDT consisting of epileptologists, neurophysiologists, neurosurgeons, radiologists and psychologists is needed to perform the procedure.
- Training in placement of DBS is necessary.
- Three Specialist Advisers thought that the procedure is likely to have a minor impact on the NHS; 1 considered the potential impact to be moderate.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent questionnaires to 1 trust for distribution to patients who had the procedure (or their carers). NICE received 1 completed questionnaire.

The Patient Commentators' views on the procedure were consistent with the published evidence and the opinions of the Specialist Advisers.

Issues for consideration by IPAC

None other than those described above.

References

1. Fisher R, Salanova V, Witt T et al. (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 51: 899–908.

2. Boon P, Vonck K, De Herdt V et al. (2007) Deep brain stimulation in patients with refractory temporal lobe epilepsy. Epilepsia 48: 1551–60.

3. Velasco AL, Velasco F, Velasco M et al. (2007) Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia 48: 1895–1903.

4. Fisher RS, Uematsu S, Krauss GL et al. (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–51.

5. Andrade DM, Zumsteg D, Hamani C et al. (2006) Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology 66: 1571–3.

6. Velasco AL, Velasco F, Jimenez F et al. (2006) Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. Epilepsia 47: 1203–12.

7. Graves NM, Fisher RS. (2005) Neurostimulation for epilepsy, including a pilot study of anterior nucleus stimulation. Clinical Neurosurgery 52: 127–33.

8. Velasco F, Velasco M, Jimenez F et al. (2002) Centromedian nucleus stimulation for epilepsy clinical, electroencephalographic, and behavioral observations. Thalamus and Related Systems 1: 387–98.

9. Miller PM, Gross RE. (2009) Wire tethering or ‘bowstringing’ as a long-term hardware-related complication of deep brain stimulation. Stereotactic and Functional Neurosurgery 87: 353–9.

Appendix A: Additional papers on deep brain stimulation for refractory epilepsy

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies. Individual case reports have not been included unless they report a safety outcome.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Andrade DM, Hamani C, Lozano A et al. (2010) Dravet syndrome and deep brain stimulation: Seizure control after 10 years of treatment. Epilepsia 51: 1314-1316.	Case series n = 2 Follow-up = 10 years	1 patient with partial onset seizures treated at age 19 showed a marked improvement in seizure control. The other patient with generalised onset treated at age 34 did not show any immediate benefit. Results may be related to age at initiation of DBS and seizure type.	Larger studies are included.
Boex C, Vulliemoz S, Spinelli L et al. (2007) High and low frequency electrical stimulation in non-lesional temporal lobe epilepsy. Seizure 16: 664–9.	Case series n = 3	High-frequency stimulation, but not low-frequency, was associated with absence of seizures in patients with non-lesional temporal lobe epilepsy.	Larger studies are included.
Boex C, Seeck M, Vulliemoz S et al. (2011) Chronic deep brain stimulation in mesial temporal lobe epilepsy. Seizure 20: 485-490.	Case series n = 8 Median follow-up = 44 months (range 12–74)	The two patients with hippocampal sclerosis obtained a significant decrease (65–75%) in seizure frequency. Two out of six patients with non-lesional epilepsy (NLES) became seizure-free, one of them without stimulation, suggesting a microlesional effect. Two NLES patients experienced reductions of seizure frequency (65–70%), whereas the remaining two showed no significant seizure reduction.	Larger studies are included.
Chabardes S, Kahane P, Minotti L et al. (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disorders 4: S83-S93.	Case series n = 5	**High-frequency stimulation of subthalamic nucleus** 3 out of 5 patients had 67–80% reduction in seizures. 1 patient responded with a weaker reduction of seizure frequency and 1 patient did not respond.	Larger studies are included.
Chkhenkeli SA, Sramka M, Lortkipanidze GS et al. (2004) Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clinical Neurology and Neurosurgery 106: 318-329.	Case series n = 54	**Included stimulation of the head of the caudate nucleus, cerebellar dentate nucleus and thalamic centromedian nucleus.** 48% (26/54) of patients were seizure-free, 43% had a worthwhile improvement. 9% (5/54) of patients had no improvement.	The main focus of the paper is on electro-physiological effects.
Franzini A, Messina G, Marras C et al. (2008) Deep brain stimulation of two unconventional targets in refractory non-resectable epilepsy. Stereotactic and Functional Neurosurgery 86: 373-381.	Case series n = 4	**Stimulation targets: posterior hypothalamus and caudal zona incerta** A significant reduction in seizure frequency was observed.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Hodaie M, Wennberg RA, Dostrovsky JO et al. (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603-608.	Case series n = 5 Mean follow-up = 15 months	**Stimulation target: anterior thalamus** Mean reduction in seizure frequency = 54%	Same patients as Andrade et al, 2006 in table 2.
Kerrigan JF, Litt B, Fisher RS et al. (2004) Electrical Stimulation of the Anterior Nucleus of the Thalamus for the Treatment of Intractable Epilepsy. Epilepsia 45: 346-354.	Case series n = 5 Follow-up = 6–36 months	**Stimulation target: anterior nucleus of the thalamus** 4 of the 5 patients showed clinically and statistically significant improvement with respect to seizure severity. 1 patient showed a statistically significant reduction in total seizure frequency.	Larger studies are included.
Khan S, Wright I, Javed S et al. (2009) High frequency stimulation of the mamillothalamic tract for the treatment of resistant seizures associated with hypothalamic hamartoma. Epilepsia 50: 1608-1611.	Case series n = 2 Follow-up = 10 months	**Stimulation target: mamillothalamic tract** Both patients had significant reduction in seizure frequency, with 1 being rendered seizure-free.	Larger studies are included.
Lee KJ, Jang KS, Shon YM (2006) Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. Acta Neurochirurgica - Supplement 99: 87-91.	Case series n = 6 Follow-up = 2–30 m	**Stimulation targets: subthalamic and anterior thalamic nuclei** Mean reduction in seizure frequency = 62%	Larger studies are included.
Lim S-N, Lee S-T, Tsai Y-T et al. (2007) Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: A long-term follow-up study. Epilepsia 48: 342-347.	Case series n = 4 Mean follow-up = 44 months	**Stimulation target: anterior thalamic nucleus** Seizure reduction = 49% (range 35–76%) 1 patient was seizure-free. 1patient had a small frontal haemorrhage and another had extension erosion over the scalp; no resultant major or permanent neurological deficit was observed.	Larger studies are included.
Osorio I, Frei MG, Sunderam S et al. (2005) Automated seizure abatement in humans using electrical stimulation. Annals of Neurology 57: 258-269.	Case series n = 8	**Closed-loop stimulation system** High-frequency stimulation was delivered directly to the epileptogenic zone (local closed-loop) or through the anterior thalamus (remote closed-loop). Mean reduction in seizure frequency = 56% for local closed-loop and 41% in remote closed-loop group.	Small case series with short-term follow-up.
Osorio I, Overman J, Giftakis J (2007) High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia 48: 1561-1571.	Case series n = 4	**Thalamic stimulation** Mean reduction in seizure frequency = 76% (range 53% to 92%). Quality of life improved in all patients.	Larger studies are included.
Shon Y-M, Kyung JL, Hye JK et al. (2005) Effect of chronic deep brain stimulation of the subthalamic nucleus for frontal lobe epilepsy: Subtraction SPECT analysis. Stereotactic and Functional Neurosurgery 83: 84-90.	Case series n = 2	**Stimulation target: subthalamic nucleus** Reduction in seizure frequency = 87% and 89%.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Taylor RB, Wennberg RA, Lozano AM et al. (2000) Central nystagmus induced by deep-brain stimulation for epilepsy..Epilepsia 41: 1637-1641.	Case report n = 1	**Nystagmus** Bilateral stimulating electrodes were implanted in the centromedian nucleus of the thalamus. Stimulation evoked nystagmus.	Nystagmus is already included in table 2 as a safety outcome.
Tellez-Zenteno JF, McLachlan RS, Parrent A et al. (2006) Hippocampal electrical stimulation in mesial temporal lobe epilepsy. Neurology 66: 1490-1494.	Double-blind, crossover RCT n = 4	**Stimulation target: hippocampus** Median reduction in seizures = 15% Effects seemed to carry over into the 'off' period.	Larger studies are included.
Velasco AL, Velasco F, Velasco M et al. (2007) The role of neuromodulation of the hippocampus in the treatment of intractable complex partial seizures of the temporal lobe. Acta Neurochirurgica - Supplement 97: 2-32.	Case series n = 9 Follow-up = 18 m	**Stimulation target: hippocampus** 5 out of 9 patients were seizure-free (all with normal MRI scan). The 4 patients with residual seizures had hippocampal sclerosis.	A similar study by the same author is included in table 2 (Velasco AL, 2007).
Velasco AL, Velasco F, Velasco M et al. (2009) Neuromodulation of epileptic foci in patients with non-lesional refractory motor epilepsy. International Journal of Neural Systems 19:139-147.	Case series n = 2	Seizure frequency was decreased >90% while preserving motor function.	Larger studies are included.
Velasco F, Velasco M, Ogarrio C et al. (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28: 421-430.	Case series n = 5 Follow-up = 3 months	**Stimulation target: centromedian thalamic nucleus** Seizures were significantly reduced. Psychological performance improved.	Larger studies are included.
Velasco F, Velasco M, Velasco AL et al. (1995) Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. Epilepsia 36: 63-71.	Case series n = 5 Follow-up = 7–33 months	**Stimulation target: centromedian thalamic nucleus** Generalised tonic–clonic seizures decreased dramatically. Other generalised seizures decreased significantly but there was no change in the number of complex partial seizures.	Larger studies are included.
Velasco M, Velasco F, Velasco AL et al. (1993) Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: II. Psychological performance and background EEG activity. Epilepsia 34: 1065-1074.	Case series n = 23	**Stimulation target: centromedian thalamic nucleus** A significant increase in psychological scores and the number of EEG waves per 10 seconds was noted.	More recent studies by the same authors are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Velasco M, Velasco F, Velasco AL et al. (2000) Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41: 158-169.	Case series n = 10	**Stimulation target: hippocampus** No evident histopathological differences were found between stimulated and nonstimulated hippocampal tissue.	Other studies from the same authors are included.
Velasco F, Velasco M, Jimenez F et al. (2000) Predictors in the treatment of difficult-to-control seizures by electrical stimulus of the centromedian thalamic nucleus. Neurosurgery 47: 295–305.	Case series n = 13	**Stimulation target: centromedian thalamic nucleus** Improvement was highly significant for generalised tonic–clonic seizures and atypical absences.	A larger more recent study from the same authors is included.
Vonck K, Boon P, Achten E et al. (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Annals of Neurology 52: 556-565.	Case series n = 3 Mean follow-up = 5 months	**Amygdalohippocampal stimulation** All 3 patients had a greater than 50% reduction in seizure frequency.	Larger studies are included.
Wille C, Steinhoff BJ, Altenmuller DM et al. (2011) Chronic high-frequency deep-brain stimulation in progressive myoclonic epilepsy in adulthood - Report of five cases. Epilepsia 52: 489-496.	Case series n = 5 Median follow-up = 24 months	**Stimulation target: subthalamic nucleus and ventral intermediate nucleus** Reduction in myoclonic seizures ranged from 30% to 100%.	Larger studies are included.

Appendix B: Related NICE guidance for deep brain stimulation for refractory epilepsy

Guidance	Recommendations
Interventional procedures	**Vagus nerve stimulation for refractory epilepsy in children. NICE interventional procedures guidance 50 (2004)** 1.1 Current evidence on the safety and efficacy of vagus nerve stimulation for refractory epilepsy in children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 The procedure should only be undertaken by specialist paediatric epilepsy teams. 1.3 Almost all the current evidence on the efficacy of the procedure relates to reducing seizure frequency only. However the effect on quality of life remains uncertain. Future audit and research should include quality of life measures. Patients, carers and children should be informed about the unpredictability of benefit. Use of the Institute's *Information for the Public* is recommended. **Deep brain stimulation for refractory chronic pain syndromes (excluding headache). NICE interventional procedures guidance 382 (2011)** 1.1 Current evidence on the safety of deep brain stimulation (DBS) for refractory chronic pain syndromes (excluding headache) shows that there are serious but well-known risks. There is evidence that the procedure is efficacious in some patients who are refractory to other forms of pain control. Therefore this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 During the consent process patients should be informed that DBS may not control their chronic pain symptoms. They should be fully informed about the possible risks associated with this procedure including the small risk of death. 1.3 DBS should only be used in patients with refractory chronic pain syndromes that other treatments have failed to control. Patient selection should be carried out by a multidisciplinary team specialising in pain management.

	Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedures guidance 381 (2011). 1.1 Current evidence on the efficacy of deep brain stimulation (DBS) for intractable trigeminal autonomic cephalalgias (TACs) is limited and inconsistent, and the evidence on safety shows that there are serious but well-known side effects. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake DBS for intractable TACs should take the following actions: • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy. They should be specifically informed that DBS may not control their headache symptoms and they should be fully informed about the possible risks associated with the procedure, including the small risk of death. Clinicians should provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/guidance/IPG381publicinfo). • Audit and review clinical outcomes of all patients having DBS for intractable TACs (see section 3.1). 1.3 Patient selection for DBS for intractable TACs should be carried out by a multidisciplinary team specialising in pain management. 1.4 Further research studies should clearly define patient selection and report the intensity and duration of stimulation, medication use and quality of life, in addition to documenting the effects on headache symptoms as clearly as possible. **Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). NICE interventional procedures guidance 188 (2006).** 1.1 Current evidence on the safety and efficacy of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Patient selection and management should be carried out in the context of a multidisciplinary team specialising in

	the long-term care of patients with movement disorders. **Deep brain stimulation for Parkinson's disease. NICE interventional procedures guidance 19 (2003)** 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.
Clinical guidelines	**Epilepsy in adults and children. NICE clinical guideline 20 (2004).** There are no recommendations relating to deep brain stimulation for refractory epilepsy.

Appendix C: Literature search for deep brain stimulation for refractory epilepsy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	29/09/2011	September 2011
Database of Abstracts of Reviews of Effects – DARE (CRD website)	29/09/2011	N/A
HTA database (CRD website)	29/09/2011	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	29/09/2011	September 2011
MEDLINE (Ovid)	29/09/2011	1948 to September Week 3 2011
MEDLINE In-Process (Ovid)	29/09/2011	September 28, 2011
EMBASE (Ovid)	29/09/2011	1980 to 2011 Week 38
CINAHL (NLH Search 2.0 or EBSCOhost)	29/09/2011	N/A
Zetoc	29/09/2011	N/A

Trial sources searched on 19/05/2011

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched on 19/05/2011

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Deep Brain Stimulation/
2	((deep or electric*) adj3 brain adj3 stimulat*).tw.
3	(dbs or dbs-stn).tw.
4	or/1-3

5	electric stimulation therapy/
6	(electric* adj3 stimulat* adj3 (therap* or treat*)).tw.
7	5 or 6
8	exp Brain/
9	brain*.tw.
10	8 or 9
11	7 and 10
12	4 or 11
13	exp Epilepsy/
14	(epileps* or epilept* or aura* or seizure*).tw.
15	(electric* adj3 hyperactiv*).tw.
16	13 or 14 or 15
17	12 and 16
18	Animals/ not Humans/
19	17 not 18