NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of deep brain stimulation for intractable trigeminal autonomic cephalalgias

Treating intense, difficult to control headache accompanied by other symptoms of the face and eyes using deep brain stimulation

Trigeminal autonomic cephalalgias (TACs) are characterised by frequent severe headache attacks that last for short periods. The headaches are usually accompanied by tears, sweating, flushing, and a runny nose on the same side of the head as the pain. Deep brain stimulation has been introduced to treat TACs that do not respond to other treatments. It aims to mask the pain by delivering electrical impulses to a precise area of the brain using an electrode.

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 2010.

Procedure name

- Deep brain stimulation for intractable trigeminal autonomic cephalalgias

Specialty societies

- Society of British Neurological Surgeons (SBNS)
- British Pain Society
- British Association for the Study of Headache.

Description

Indications and current treatment

Trigeminal autonomic cephalalgias (TACs) (including cluster headache, hemicranias continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing [SUNCT] and paroxysmal hemicranias) are characterised by relatively short-lasting but severe pain attacks associated with oculofacial autonomic manifestations such as tearing, sweating, flushing, and rhinorrhea on the same side of the head as the pain.

Cluster headache (CH) is the most common form of TAC, and is characterised by sudden onset symptoms lasting up to 3 hours several times a day, for several days or weeks, occurring in clusters of a few months. The syndrome can be episodic with periods of remission which can last several years, but the chronic form is characterised by a lack of significant remission periods. SUNCT and paroxysmal hemicranias are distinguished from cluster headaches by shorter attacks that are less responsive to therapy.

Medical therapy, either to prevent or abort episodes, is usually the first-line treatment for TACs. Surgery to interrupt the trigeminal sensory or autonomic pathways is sometimes used, but complications may be severe, including diplopia, hyperacusia, jaw deviation, corneal anaesthesia, corneal ulcers, and anaesthesia dolorosa.

What the procedure involves

Deep brain stimulation (DBS) has been introduced as an option for relief of TAC pain where alternative treatments have failed. It involves stereotactic targeting of specific anatomical sites within the brain in order to modulate the central processing of pain signals and improve the patient's symptoms. The posterior hypothalamic region ipsilateral to the pain is often the target area for stimulation in keeping with imaging studies that demonstrate activity in this region during TACs.

The procedure takes place in two stages. Using magnetic resonance imaging (MRI) and/or computed tomography (CT) images to guide positioning, electrodes are inserted into the brain (through small holes drilled into the skull) usually under local anaesthetic and/or intravenous sedation. A test stimulation (or macrostimulation) is used to check for side effects. Postoperative scans are sometimes used to assess the position of electrodes and to avoid complications such as local haemorrhage. Following satisfactory electrode placement and testing, a pulse generator connected by tunnelled wires to the electrode is implanted under the chest wall usually with the patient under general anaesthesia. Usually, the generator remains switched 'on'.

Disease classification systems

The International Classification of the Headaches Disorders (ICHD-II) criteria defines chronic cluster headache as 'Cluster headache attacks occurring for

more than 1 year without remission or with remissions lasting less than 1 month.'

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to Deep brain stimulation for deep brain stimulation for intractable trigeminal autonomic cephalalgias. Searches were conducted of the following databases, covering the period from their commencement to 23 November 2010: 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 intractable trigeminal autonomic cephalalgias
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 45 patients from 1 randomised-controlled trial[1] and 4 case series[2,3,4,5].

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 intractable trigeminal autonomic cephalalgias

Abbreviations used: CH, cluster headache; CI, confidence interval; CT, computer tomography; DBS, deep brain stimulation; HAD, Hospital anxiety and depression scale; ICHD-II, International Classification of the Headaches Disorders; MRI, magnetic resonance imaging; SF, short form; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V, voltage

Study details	Key efficacy findings	Key safety findings	Comments
Fontaine D (2010)[1] **Crossover RCT (double blind)** France Recruitment period: 2005–2007 Study population: refractory chronic CH n = **12 (5 DBS then sham [group A] vs 6 sham then DBS [group B])** 1 declined to participate Mean age: 44.1 years, Sex: 72.7% male, Mean disease duration: 12.1 years, CH characteristics: 6 chronic, 5 episodic, 5 left, 6 right, Mean attack duration per week: 17.8 Patient selection criteria: met ICHD-II criteria for chronic CH, disease duration > 3 years, drug resistant, daily attacks, age 18–65	Number of patients analysed: **11 (group A, 5 vs group B, 6)** ***RCT phase*** (Stimulation voltage during this phase ranged between 1.0 and 2.8 V) **Headache outcomes** Group mean and 95% CI. P values represent difference between groups when on or off stimulation. Outcome | Difference between active and sham in on-off group | Difference between active and sham in off-on group | p value Attacks per week | 0.2 (-24.0 to 23.6) | -2.7 (-25.7to 20.31) | 0.927 Pain intensity* | 0 (-1.4 to 1.4) | 0.3 (-9.5 to 10.0) | 0.357 *Based on Likert scale (1 to 7 scale, with higher values indicating more pain). **Medication usage** Outcome | Difference between active and sham in on-off group | Difference between active and sham in off-on group | p value injections per week | 2 (-9.0 to 13) | -5.3 (-24.1 to 13.5) | 0.349 **Emotional and general health outcomes** Outcome | Difference between active and sham in on-off group | Difference between active and sham in off-on group | p value Patient impression of change [a] | 0.8 (-20.1 to 21.8) | 1.3 (-4.2 to 6.8) | 0.835 HAD Anxiety [b] | 0.2 (-23.6 to 24.0) | -2.6 (-25.5 to 20.3) | 0.927 HAD Depression [b] | 1.3 (-22.4 to 25.1) | 5.3 (-1.08 to 11.7) | 0.154 SF mental score [c] | 5.8 (-12.8 to 24.4) | -8.7 (-27.3 to 9.9) | 0.197 SF physical score [c] | -3.9 (-13.1 to 5.3) | 2.8 (-15.4 to 21.0) | 0.197 [a] 7-point scale, with lower numbers indicating greater improvement. [b] HAD has 7 anxiety items and 7 depression items, with scores greater than 7 indicating anxiety and depression, respectively. [c] Lower numbers indicate greater disability.	***Series adverse events*** 3 series events were reported in 2 patients: - subcutaneous infection 3 weeks after surgery which resolved after hardware removal and antibiotic treatment. Patient was re-implanted 6 months later - preoperative loss of consciousness with hemiparesis shortly after test stimulation. CT scan was normal and symptoms spontaneously resolved in 2 hours with no sequelae. During the open period, the same patient also had multiple severe micturition syncopes associated with a decrease in blood pressure in the standing position (no further details given). ***Non-serious adverse events*** 26 events occurred. All were mild and most were transient. Rates similar in both on and off periods. **Event** | **No. of patients** *Related to surgery:* Neck pain along lead | 1 *Transient related to test stimulation:* Complex oculomotor disturbances[a] | 4 *During 'on' period:*	**Follow-up issues**: • 1 patient declined to participate before randomisation. **Study design issues**: • 4 academic centres. • Recruitment not described. • Block randomisation performed centrally. • Patients unable to feel if stimulator was on or off; clinical evaluation by neurologist blind to stimulation status. • 1 month treatment period determined from existing evidence showing response within 1 to 4 weeks. • Authors did not detect a carry-over effect indicating adequacy of 1 week wash-out period (not described how this was measured). • Used intention to treat analysis. • Power calculation based on estimate

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Study details	Key efficacy findings	Key safety findings	Comments

years, normal MRI findings

Exclusion criteria: substance abuse or dependence, contraindication to surgery or anaesthesia

Technique: DBS with Medtronic system; for first 2 months, groups alternated electrode 'on' phase (1 month each) with 1 week wash-out period, (185 Hz, 60 µS, 3 V or 80% of threshold producing side effects). For next 10 months, all patients had electrode turned 'on' ('open phase')

Follow-up: **1 year**

Conflict of interest/source of funding: Medtronic (who sold the stimulators) provided funds for meetings of the investigators but had no other role.

Open phase

Headache outcomes Group median and range

Outcome	Baseline	1 year	p value
Attacks per week [a]	14 (7 to 53)	8 (0 to 23)	0.082
Pain intensity [b]	6 (2 to 10)	4.5 (0 to 10)	0.499

[a] This represents a 48.4% decrease in mean weekly attack frequency; 54.5% (6/11) had at least a 50% decrease in attacks (called 'responders'); 3 patients were pain-free.
[b] Based on Likert scale (1 to 7 scale, with higher values indicating more pain).

Medication usage

Outcome	Baseline	1 year	p value
Injections per week	1 (0 to 15)	0.5 (0 to 26)	0.288

Emotional and general health outcomes

Outcome	Baseline	1 year	p value
HAD Anxiety [a]	13 (5 to 18)	7.5 (0 to 14)	0.008
HAD Depression [a]	10 (1 to 16)	4.5 (1 to 15)	0.052
SF mental score [b]	33.2 (27.5 to 53.3)	37 (20.7 to 56.6)	0.953
SF physical score [b]	32.7 (24.4 to 46.5)	39.7 (25.2 to 50.5)	0.173

[a] HAD has 7 anxiety items and 7 depression items, with scores greater than 7 indicating anxiety and depression, respectively.
[b] Lower numbers indicate greater disability.

Among the 6 responders, prophylactic treatment was stopped or the dose was decreased in 2, unchanged in 2 and modified in 2. Additionally, 63.6% (7/11) patients reported a 'calming effect' compared to baseline.

Mild hunger increase	3
Mild hunger decrease	1
Mild libido decrease	2
During 'off' period:	
Mild hunger increase	2
Mild hunger decrease	1
Mild thirst increase	1
Mild thirst decrease	1
Mild libido decrease	1
Increased testosterone level	1
Shortened menstrual cycle	1
During 'open' phase:	
Facial flush attacks	1
Changes in blood pressure in response to posture	1
Moderate weight increase (5 kg)	1
Mild hunger increase	1
Mild hunger decrease	1
Mild libido decrease	1
Increased testosterone level	1
TOTAL	26

[a] 3 reported transient diplopia, 1 reported impairment of gaze fixation without objective oculomotor paresis.

that mean weekly frequency of attacks at baseline would be 23.9; overall power of 90% to detect a 50% reduction in number of attacks during the last week of each stimulation period.

- Stimulation parameters could be changed during the 'open' phase.

Study population issues:

- No differences between groups.
- Patients continued on prophylactic treatment, although some decreased treatments during the open phase (see efficacy column).

Other issues:

- Authors considered reasons for no treatment affect in randomisation phase may have included sample size, delay in therapeutic effect, and stimulation parameters used during this phase.

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Study details	Key efficacy findings	Key safety findings	Comments
Broggi G (2007)[2] **Case series** Italy Recruitment period: 2000–2007 Study population: refractory chronic CH (n = 16), SUNCT (n = 1), atypical facial pain (n = 3) n = **20 (16 chronic CH, 1 SUNCT, 3 atypical facial pain)** Characteristics of patients with CH mean age: 43 years Sex: 87.5% male 2 bilateral, mean 3.3 years duration of chronic CH (all had chronic CH for at least 1 year), mean 7 attacks per day Characteristics of patient with SUNCT – 66-year-old woman with 14-year history of unilateral, short-lasting, severe pain episodes Characteristics of 3	Number of patients analysed: **20 (16 chronic CH, 1 SUNCT, 3 atypical facial pain)** ***Affect on chronic CH (n = 16)*** One patient required another implant at different coordinates because there was no improvement after the first implant. Stimulation was 'on' for a mean of 17.6 months at a mean amplitude of 2.4 V. Resolution of headache: At mean follow-up of 23 months, all 16 patients achieved pain relief. Thirteen patients were considered to have had major improvements in pain: 10 were considered pain-free but 3 still had sporadic attacks. Of the remaining 3 patients, 1 had a reduction in the number of attacks per day from 5 to 1, 1 had a reduction in pain intensity from excruciating to mild and with a shorter duration (from 90 to 15 minutes) and 1 had a reduction in attacks from 7 per day to 1 attack every 2 days (patient who required second implant). **Mean (range)** Time to response (days)* 42 (1 to 86) % of pain-free days 71 (27 to 98) * One patient with only 1 month of follow-up was unable to have sufficient evaluation. Four patients had their stimulation turned off for unrelated issues; pain attacks recurred after a few days and disappeared a few hours after the generator was reactivated. Requirement for prophylaxis: 2 patients who were considered pain-free had methysergide (2–3 mg/day and verapamil 360 mg), 2 patients with sporadic attacks had verapamil (360 and 480 mg), and 1 patient with an attack every 2 days had methysergide (3 mg) and verapamil (360 mg) (this was the patient who required the second implant). ***Affect on SUNCT (n = 1)*** The patient was first treated with bipolar stimulation but this was not effective so unipolar stimulation was started after 15 days. Pain attacks subsided after 1 month at 0.9 V but reappeared 3 months later. After an increase of amplitude (to 1.8 V), pain subsided. Eight months after implantation, the stimulator was turned off (patient was blind to this) and the patient remained pain-free for 3 months but the attacks gradually reappeared again. The stimulator was turned on again and the pain subsided. Fifteen months after implantation, the patient started experiencing sporadic attacks which was treated successfully with 100 mg/day of lamotrigine. ***Affect on atypical facial pain (n = 3)***	***Adverse events*** - One patient with chronic CH had the electrode removed because of deep infection and recovered completely without neurological deficits. - One patient treated for CH had cranial migration which required electrode replacement after 1 year. - One patient treated for CH had mild, unsymptomatic haemorrhage of the posterior wall of the third ventricle. This was observed on routine postoperative CT. - Of the 16 patients treated with chronic CH, 4 had asymptomatic orthostatic hypotension detected during routine monitoring within 24 hours of the procedure. - The patient treated for SUNCT had transient difficulties in conjugated eye movements when the amplitude was increased to 1.4 V.	**Follow-up issues**: • Not reported. **Study design issues**: • Selection of patients not described; patients were told about alternative treatments so it appears they may have been self-selected. **Study population issues**: • Atypical facial pain was caused by radical transmandibular tumour resection, after minor dental procedure, and after radiotherapy for rhinopharynx carcinoma. **Other issues**: • There are several publications including some or all of the 16 patients treated for chronic CH. These are included in

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Study details	Key efficacy findings	Key safety findings	Comments
patients with atypical facial pain – 2 male (aged 47 and 55 years), 1 female (aged 52 years) Patient selection criteria: normal neurological examination and cerebral MRI, psychologically stable. Technique: DBS with Medtronic system; stimulation at 180 Hz, 60 µs, 1-3 V Mean follow-up: **23 months for chronic CH; not reported for other indications)** Conflict of interest/source of funding: not reported.	These patients had a moderate reduction in pain after the operation, but after 4 months of continuous stimulation, the pain returned to preoperative levels. Increases in amplitude or bipolar stimulation did not have any effect on pain. The pulse generator was blindly switched off; episodes of paroxysmal pain were described as slightly more severe than those during stimulation.		appendix A.

Abbreviations used: CH, cluster headache; CI, confidence interval; CT, computer tomography; DBS, deep brain stimulation; HAD, Hospital anxiety and depression scale; ICHD-II, International Classification of the Headaches Disorders; MRI, magnetic resonance imaging; SF, short form; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V, voltage

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Schoenen J (2005)[3]

Case series
Belgium
Recruitment period: not reported
Study population: patients with unilateral refractory chronic CH
n = 6
Mean age: 46.7 years
Sex: 83% male
Mean disease duration: 6.7 years (range: 3–10 years) with mean 4.5 years in the chronic phase (range: 2–9 years)
Attack frequency per day was from 1 to 7
Patient selection criteria: aged 25 to 55 years for at least 2 years with 4 or more disabling side-locked attacks per week, resistance or intolerance to adequate trials of steroids, verapamil,</td>
<td>Number of patients analysed: 5 (1 patient excluded because the patient with the adverse event during implantation of the electrode – as listed in safety column – and subsequently did not receive the implant)
Resolution of headache
Frequency, intensity, autonomic symptoms and adverse events recorded in patient diaries.
All patients improved in the 2 weeks after the operation.
<table>
<tr><th>Patient</th><th>Outcomes</th><th>Follow-up</th></tr>
<tr><td>1</td><td>Unstable for 7 months
Pain-free for 5 months (after change to bipolar plot combination)
Recent relapse of daily attacks</td><td>17 months</td></tr>
<tr><td>2</td><td>Relief for 8 months
Pain-free for last 5 months</td><td>15 months</td></tr>
<tr><td>3</td><td>Relief for 8 months (attacks reduced and treated with sumatriptan)
Relapse (treated with change in stimulation parameters)
Pain-free for the last 4 months</td><td>14 months</td></tr>
<tr><td>4</td><td>Pain-free for 9 months
Pain-free for 3 months
Relapse*
Pain-free for the last 3 months</td><td>12 months</td></tr>
<tr><td>5</td><td>Did not receive the procedure because of safety events (see safety column)</td><td>n/a</td></tr>
<tr><td>6</td><td>Died (see safety column)</td><td>n/a</td></tr>
</table>
* One patient consented to the generator being turned off after a pain-free period of 3 months in order to test the effects. This relapse in pain attacks occurred when the stimulator was switched off and stopped after it was turned on again.
Of the four who had implantation and stimulation, the clinical outcome at the writing of the study was excellent for 3 (2 were pain-free and one had less than 3 attacks per month) but unsatisfactory in one who had transient remissions.</td>
<td>Adverse events
1 patient died 3 days after the procedure from an intracerebral haemorrhage. During the procedure, the patient had moderate hypertension and an attack that was treated with 1 mg intravenous dihydroergotamine. Five hours later the patient became comatose and angiography showed a saccular aneurysm on the superacavernous portion of the left carotid artery. Post-mortem showed no other vascular changes.

1 patient had a panic sensation with tachypnoea, tachycardia and moderate hypertension during the procedure. After the operation was interrupted and the recording electrode was removed, the patient's vital parameters returned to normal.

All patients had diplopia and dizziness if high</td>
<td>Follow-up issues:
• One patient lost to follow-up.

Study design issues:
• Includes 2 patients selected from a national waiting list and 4 recruited over a 6-month period.

Study population issues:
• All patients were resistant to available preventive treatments, including to changes made in the 1–3-month period that they waited before the operation.

Other issues:
• In the patient who died, vasculopathy because of the daily use of narcotics for the preceeding year was ruled out with histological</td>
</tr>
</table>

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Study details	Key efficacy findings	Key safety findings	Comments
methysergide, lithium and/or ergotamine and no other disabling medical or psychiatric disorders. Technique: DBS with Medtronic system; 180 Hz, 1–3 V, pulse width 60 µs; generator was switched on as soon as attack occurred. Mean follow-up: **14.5 months** Conflict of interest/source of funding: device provided by Medtronic.		stimulus intensities were reached (above 1.5 V). When mild, they usually disappeared after 24 to 48 hours (details of moderate or severe diplopia not reported).	examination. • Authors noted that the patient who had the panic attack seemed excessively anxious and stressed before the operation.

Abbreviations used: CH, cluster headache; CI, confidence interval; CT, computer tomography; DBS, deep brain stimulation; HAD, Hospital anxiety and depression scale; ICHD-II, International Classification of the Headaches Disorders; MRI, magnetic resonance imaging; SF, short form; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V, voltage

Study details	Key efficacy findings	Key safety findings	Comments
Bartsch T (2008)[4] **Case series** Germany Recruitment period: not reported Study population: patients with unilateral chronic CH n = **6** Mean age: 40 years Sex: 66.7% male Years with chronic condition: 7 (range: 2–16) Attack frequency per day: from 1–2 to 4–-8 Patient selection criteria: met International Headache Society criteria for chronic CH and criteria proposed by Leone (included in Broggi[2]) and no etiological factors identified on MRI, CSF analysis, ultrasound, blood, physical or psychiatric testing	Number of patients analysed: **6** ***Frequency and intensity of headache*** <u>Short-term</u> All showed decrease in attack frequency, but 4 had a 90–100% decrease in attack frequency in the first few weeks; 2 had only a marginal, non-significant decrease (less than 30% in frequency) within the first weeks after the procedure before returning to baseline levels. Of the 4 with a profound decrease, the pain intensity of the remaining attacks was significantly lower on the VAS (10 out of 10 at baseline to 1 or 4 out of 10). <u>Long-term</u> In 2 of the 4 with a profound response to treatment, adjustments in the amplitude and pulse width were required to maintain the stimulation effect. In 1 of the 4 patients, attacks returned at the same level as at baseline at 6 months and the procedure was aborted. At mean follow-up of 17 months, 3 were almost completely attack free in the 9 to 15 months after DBS. In the 2 with marginal transient effects, adjustments were made over 17 months but there was no longer-lasting effect. During the reprogramming, the stimulation device was switched off twice in these patients with a reported marginal short-lasting worsening of the pain. ***Affect on daily life and activity and quality of life*** Preoperative testing showed that headaches had a considerable impact on daily life and activity of the 2 patients, who were later reported to have marginal transient effects of stimulation (assessed on Headache Impact Test-6: 70/78 and 70/78, and Henry Ford Headache Disability Inventory: 72/100 and 67/100). These patients also had an affective component (assessed on Beck depression inventory scores [scale 0 to 68 with 0 indicating no depression]: 4 and 22 and SF-36: 10/11 and 11/11). Postoperative values not reported in these patients (but, as these patients had minimal effects, these are presumed to have not changed dramatically). Two of the 4 patients with a profound effect on frequency and intensity of attacks after stimulation were reported to have had a tendency for improvement in quality of life after assessment (measured on SF-36 – scores not reported). These patients were also reported to have had normal values in the Hamilton depression scale after the procedure (postoperative values 4 and 6 reported by the study but preoperative scores not reported; Hamilton depression scale is a 17-item scale, 0 – 54 with scores over 24 indicating severe depression, 18 to 24 indicating moderate depression, 7 to 17 indicating mild depression and 0 to 6 indicating a normal person with regard to depression). Autonomic functions such as sleep, body weight, personality or eating behavior did not show changes.	***Adverse events*** Only transient and mild side-effects were noted. Short-lasting vertigo and transient double vision were most common. One patient had an intraoperative cluster attack which was elicited by the test stimulation.	**Study design issues**: • 4 centres. • Team of neurologists specialising in headache did patient selection. • Pain diary was used to record attack frequency and pain intensity including autonomic characteristics in the 4 months before and then afterwards.

Abbreviations used: CH, cluster headache; CI, confidence interval; CT, computer tomography; DBS, deep brain stimulation; HAD, Hospital anxiety and depression scale; ICHD-II, International Classification of the Headaches Disorders; MRI, magnetic resonance imaging; SF, short form; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V, voltage

Study details	Key efficacy findings	Key safety findings	Comments
Technique: DBS with Medtronic system; mean 17 Hz, between 1.5 and 4 V Mean follow-up: **17 months** Conflict of interest/source of funding: not reported.			

Abbreviations used: CH, cluster headache; CI, confidence interval; CT, computer tomography; DBS, deep brain stimulation; HAD, Hospital anxiety and depression scale; ICHD-II, International Classification of the Headaches Disorders; MRI, magnetic resonance imaging; SF, short form; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V, voltage

Study details	Key efficacy findings	Key safety findings	Comments
Starr PA (2007)[5] **Case series** USA Recruitment period: not reported Study population: patients with medically intractable CH n = **4** Mean age: 54.8 years Sex: not reported Mean years with condition: 18.9 (range: 12 to 37) Mean number of attacks per week: 25.5 (range: 13–51) Mean duration of attacks: 18.9 minutes (range: 5–38) Patient selection criteria: meeting ICHD diagnostic criteria for CH, chronic or severe episodic CH for at least 6 months of the year for at least 2 years, at least 7 debilitating	Number of patients analysed: **4** ***Occurrence of headache*** 2 patients were considered 'responders' (had 50% or more reduction in intensity of frequency). One 'non-responder' had complete suppression of headaches for 1 to 2 weeks after each reprogramming session but no persistent improvement or reduction in abortive therapy. The other 'non-responder' had modest reduction in headache intensity but the reduction did not reach 50%.	***Adverse events*** One patient had an intraoperative transient ischaemic attack which occurred 5 minutes after the test stimulation. It resolved completely in 5 minutes. Emergency head CT showed no haemorrhage and subsequent MRI showed no diffusion abnormalities or abnormalities in the intracranial vessels. The DBS tip was slightly deep to the target and had exited the floor of the third ventricle and terminated within the interpeduncular cistern near the midline. Authors hypothesised that a spasm may have been induced from the test stimulation.	**Study design issues**: • Patients screened by neurologist. • Intensity, frequency and severity measured throughout a 1-week period in patient diaries before surgery and after 1 year of continuous stimulation. • Patients recorded attack frequency and intensity in diaries.

Case no.	Headache at baseline (in 1 week previous to treatment)			Headache at 12 months		
	No. of headaches/week	Mean duration (min)	Mean intensity [a]	No. of headaches/week	Mean duration (min)	Mean intensity [a]
1 [b]	13	38	6.7	12	35	2.5
2 [b]	22	16	4.9 [c]	4	22.5	2.5
3	16	5	7.5	16	10	7.5
4	51	16	6.4	56	5	4.0

[a] Measured on 1 to 10 VAS with higher score being worst pain.
[b] Patients considered 'responders' (> 50% improvement in frequency and intensity).
[c] Measured during less intense time.

Medication requirements

Case no.	Medications in week before treatment (mg/day)		Medication s at 12 months (mg/day)	
	Prophylactic	Abortive	Prophylactic	Abortive
1 [a]	Hydrocodone (45)	None	Hydrocodone (45)	None
2 [a]	Levetiracetam (1000)	Oxygen, sumatriptan [b]	Levetiracetam (500)	None
3	Prednisone (10–60), verapamil (1200), lithium (1200), frovatriptan (5)	Sumatriptan [b]	Verapamil (960), lithium (600), frovatriptan (10)	Sumatriptan [b]

Abbreviations used: CH, cluster headache; CI, confidence interval; CT, computer tomography; DBS, deep brain stimulation; HAD, Hospital anxiety and depression scale; ICHD-II, International Classification of the Headaches Disorders; MRI, magnetic resonance imaging; SF, short form; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V, voltage

Study details	Key efficacy findings	Key safety findings	Comments
headaches per week (at least 6 on a VAS from 1 to 10), prophylactic therapy had failed, abortive therapy such as oxygen, sumatriptan and opiates failed Technique: DBS with Medtronic system; monopolar stimulation with 1–3 V, 60 µs, 185 Hz Mean follow-up: **1 year** Conflict of interest/source of funding: two authors received honoraria and research funding from Medtronic	4 | Prednisone (60), Depakote (1000) | None | Depakote (1000), Methergine | None [a] Patients considered 'responders' (> 50% improvement in frequency and intensity). [b] Subcutaneous 6.		

Efficacy

Effect on headache

A randomised crossover study of 12 patients with chronic cluster headache (CH) reported that there was no significant difference between the periods when the device was switched 'on' and when it was switched 'off' in either the 'on then off' group or the 'off then on' group for a number of outcomes including frequency of attacks, pain intensity (measured on the Likert scale, which ranges from 1 to 7, with 7 indicating more pain), patient satisfaction (on Patients' Global Impression of Change 7-point scale, with 1 indicating best improvement) or emotional impact (measured on the Hospital Anxiety and Depression Scale [HAD])[1].

The study then included a 10-month open phase when all patients received DBS. At the end of the 10 months, the mean weekly attack frequency decreased by 48% from baseline (from 14 to 8 attacks per week; p = 0.08).

A case series of 20 patients reported that all 16 patients treated for chronic cluster headache had pain relief at a mean follow-up of 23 months. Time to response occurred at a mean of 42 days (range 1 to 86 days) with mean 71% of pain-free days. The same study reported that 1 patient with short-lasting unilateral neuralgiform headache attacks and 3 patients with atypical facial pain had initial success after DBS but this failed to relieve pain in the longer term[2].

A case series of 6 patients with CH reported that, of the 4 who were successfully treated with the procedure, all improved in the 2 weeks after the operation. At a mean follow-up of 14.5 months, the clinical outcome was excellent for 3 patients (2 were pain-free and 1 had less than 3 attacks per month) but unsatisfactory in 1, who had transient remissions[3].

Another case series of 6 patients with CH reported that all patients had a decrease in attack frequency after the procedure. However, 4 were considered to have had a more profound response – a 90–100% decrease in attack frequency in the first few weeks and a reduction in the intensity of the remaining attacks from 10 at baseline to 1 or 4 at follow-up (measured on 10-point VAS, with 10 being worst pain). In 1 of these patients, attacks returned at 6 months and stimulation was aborted. At mean follow-up of 17 months, 3 patients were almost completely attack free, but the 2 with marginal transient effects did not have improvements despite adjustments in the stimulation parameters[4].

Affect on anxiety and depression and quality of life

The crossover RCT reported significantly reduced anxiety and depression scores measured on the HAD (7 anxiety items and 7 depression items with scores greater than 7 indicating anxiety and depression, respectively) in the 'open' phase only. Anxiety scores decreased from 13 to 7.5 (p = 0.008) and depression scores decreased from 10 to 4.5 (p = 0.052)[1].

A case series of 6 patients reported that 2 of the 4 patients who had a profound response to treatment had a tendency for improvement in quality of life after assessment as measured on the Short Form (36) health survey (SF-36), and normal postoperative values of 4 and 6 in the Hamilton depression scale (scores for SF-36 not reported and preoperative values in the Hamilton depression scale not reported; Hamilton depression scale is a 17-item scale, 0–54 with scores over 24 indicating severe depression)[4].

Safety

Death

In a case series of 6 patients with chronic CH, 1 patient died 3 days after the procedure from an intracerebral haemorrhage which developed along the lead tract a few hours after the procedure[3].

Other

The crossover RCT of 12 patients with chronic CH reported subcutaneous infection 3 weeks after surgery in 1 patient, which resolved after hardware removal and antibiotic treatment. Another patient lost consciousness with hemiparesis shortly after test stimulation but symptoms resolved spontaneously in 2 hours with no sequelae. However, during the open period, the same patient also had multiple severe micturition syncopes associated with a decrease in blood pressure in the standing position (no further details given)[1].

The case series of 4 patients reported a transient ischaemic attack 5 minutes after the test stimulation in 1 patient, which resolved without sequelae within 5 minutes. Authors hypothesised that a spasm causing the electrode tip to exit the floor of the third ventricle may have been induced from the test stimulation[5].

The RCT of 12 patients reported increased testosterone level (n = 1) and shortened menstrual cycle (n = 1) during the ‘off’ period. Mild increases or decreases in hunger, thirst and libido were reported in up to 8 patients during the ‘on’ and ‘off’ periods and the ‘open’ phase (there was no difference in rate of non-serious adverse events between the different phases)[1].

The case series of 20 patients reported 1 event each of deep infection requiring electrode removal (with complete recovery), cranial electrode migration requiring replacement after 1 year and mild, asymptomatic haemorrhage of the posterior wall of the third ventricle observed on routine postoperative CT, and transient difficulties in conjugate eye movements when the amplitude was increased (in the patient with SUNCT)[2].

One patient in the case series of 6 patients with CH reported panic sensation and had tachypnoea, tachycardia and moderate hypertension during the procedure. The operation was interrupted and the recording electrode was removed; the patient’s parameters returned to normal[3].

Validity and generalisability of the studies

- There was 1 small crossover RCT[1], but the other were case series.
- There are small numbers of patients.
- The RCT treated the patients in the stimulation 'on' phase for 1 month only. However, the largest case series (n = 16 patients treated for chronic CH[2]) reported that time of response to treatment occurred at a mean 42 days after stimulation. This may explain why there were no differences in effect between the 1 month 'on' and 'off' phases in the RCT.
- The criteria to determine if patients were drug-resistant or refractory to other treatments varied between the RCT and the other studies. The patients included in the RCT had not tried as many alternative treatments as the patients in most of the case series.

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

- Deep brain stimulation for Parkinson's disease. NICE interventional procedures guidance 19. Available from www.nice.org.uk/guidance/IPG19
- Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). NICE interventional procedures guidance 188. Available from www.nice.org.uk/guidance/IPG188

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.

Dr Anish Bahra, British Association for the Study of Headache, Professor Tipu Aziz, Mr Alex Green, Mr Manjit Matharu, Mr Ludvic Zrinzo, Society of British Neurological Surgeons.

- Three Advisers perform this procedure for a variety of conditions. Two only refer patients for the procedure.
- The comparator is medication.
- Anecdotal adverse events or those reported in the literature include death, stroke, infection, seizures, and visual disturbance.

- Anecdotal adverse events occurring with DBS for other indications include wire breakage and displacement.
- Theoretically, the various functions modulated by the hypothalamus could be affected, such as a change in mood or endocrine status.
- Key efficacy outcomes include headache scoring systems based on the number of headaches, severity and length of attacks and quality of life.
- Advisers considered that this can be a highly effective procedure compared with medication in some patients but that it should be considered the last resort because of the potential risks.
- A functional neurosurgical service with well-trained neurosurgeons is required to undertake this procedure safely.
- Advisers commented that there is controversy regarding the use of microelectrode recording during DBS and whether or not it increases the risk of bleeding.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent 23 questionnaires to 1 trust for distribution to patients (or their carers) who had DBS for chronic pain (including headache). NICE received 11 completed questionnaires, 3 related to TACs.

The Patient Commentators raised the following issues which did not feature in the published evidence or the opinions of Specialist Advisers, and which the Committee considered to be particularly relevant:

- All 3 patients who had DBS for TACs reported improvements in quality of life and were no longer suicidal after receiving treatment, even if pain was relieved only partially.

Issues for consideration by IPAC

- Because of the significant impact of the condition on daily activities of life, individuals with TACs are likely to be considered to have a disability by the Disability Discrimination Act.

References

1. Fontaine D, Lazorthes Y, Mertens P et al. (2010) Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. Journal of Headache and Pain 11:21–31.

2. Broggi G, Franzini A, Leone M et al. (2007) Update on neurosurgical treatment of chronic trigeminal autonomic cephalalgias and atypical facial pain with deep brain stimulation of posterior hypothalamus: results and comments. Neurological Sciences 28: Suppl. 45.

3. Schoenen J, Di CL, Vandenheede M et al. (2005) Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 128: 4–7.

4. Bartsch T, Pinsker MO, Rasche D et al. (2008) Hypothalamic deep brain stimulation for cluster headache: experience from a new multicase series. Cephalalgia 28: 285–95.

5. Starr PA, Barbaro NM, Raskin NH et al. (2007) Chronic stimulation of the posterior hypothalamic region for cluster headache: technique and 1-year results in four patients. Journal of Neurosurgery 106: 999–1005.

Appendix A: Additional papers on deep brain stimulation for intractable trigeminal autonomic cephalalgias

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.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Andy OJ (1989) Post concussion syndrome: brainstem seizures, a case report. Clinical Electroencephalography 20: 24–34.	Case report n = 1 after car accident had extraocular nerve palsy in right 3rd, 4th and 6th nerves resulting in severe headaches, irritability, absence attacks etc Follow-up = > 18 months	Patient no longer suffers from severe headaches and other accident-related problems (irritability, absence attacks, memory impairment, double vision, confusion, nervous attacks, loquaciousness and insomnia).	Larger studies included in table 2.
Brittain JS, Green AL, Jenkinson N et al. (2009) Local field potentials reveal a distinctive neural signature of cluster headache in the hypothalamus. Cephalalgia 29: 1165–73.	Case series n = 2 with cluster headache Follow-up = 10 and 11 months	1 patient had near total relief at 10-month follow-up 1 had reduced frequency after post-surgical hiatus and massively reduced severity at 1-month follow-up.	Larger studies included in table 2.
Fontaine D, Lanteri-Minet M, Ouchchane L et al. (2010) Anatomical location of effective deep brain stimulation electrodes in chronic cluster headache. Brain 133 (Pt:4) 1214–23.	Prospective RCT (but outcomes only in open phase) n = 10 with chronic cluster headache Follow-up = 1 year	There was no significant difference between the contact coordinates and the structures between those who responded to treatment (n = 5) and those who did not.	Patients included in RCT in table 1[1] for both the cross over and open phase.
Franzini A, Ferroli P, Leone M et al. (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52: 1095–9.	Case series n = 5 with chronic intractable cluster headache Follow-up = 2 to 22 months	All patients were pain-free, 2 without any medication but 3 required low doses of methysergide or verapamil.	Updated publications from this centre have included these patients, including a study in table 2[2].
Franzini A, Ferroli P, Leone M et al. (2004) Hypothalamic deep stimulation for the treatment of chronic cluster headaches: a series report. Neuromodulation 7: 1–8.	Case series n = 8 with chronic intractable cluster headache Follow-up = 1 to 26 months	All 8 patients have improved, and steroid administration has been withdrawn progressively. 3 were pain-free without medication but 5 required low doses of methysergide and/ or verapamil.	Updated publications from this centre have included these patients, including a study in table 2[2].
Green AL, Nandi D, Armstrong G et al. (2003) Post-herpetic trigeminal neuralgia treated with deep brain stimulation. Journal of Clinical Neuroscience 10: 512–4.	Case report n = 1 with right-sided facial dysaesthesia after shingles 10 years earlier refractory to pharmacological therapy Follow-up = 6 months	Patient was pain-free at last follow-up.	Larger studies included in table 2.

Leone M, Franzini A, Broggi G et al. (2003) Hypothalamic deep brain stimulation for intractable chronic cluster headache: a 3-year follow-up. Neurological Sciences 24: Suppl. 5.	Case series n = 7 with intractable chronic cluster headache Follow-up = 3 to 33 months	No more pharmacological therapy necessary in 6 patients because they were pain-free. One had attacks again in the last 3 months after an 18-month pain-free period. In 4 patients, turning the stimulator off and then on stimulated the reappearance and disappearance of pain attacks.	Updated publications from this centre have included these patients, including a study in table 2[2].
Leone M, Franzini A, Broggi G et al. (2004) Long-term follow-up of bilateral hypthalmic stimulation for intractable cluster headache. Brain 127: 2259–64.	Case report n = 1 with intractable cluster headache Follow-up = 42 months (left) and 31 months (right)	First patient reported on. Patient remains crisis-free without need for pharmacological prophylaxis. Transient vertigo and bradycardia were the only side effects.	Larger studies included in table 2.
Leone M, Franzini A, Broggi G et al. (2006) Acute hypothalamic stimulation and ongoing cluster headache attacks. Neurology 67: 1844–5.	Case series n = 16 with drug-resistant chronic cluster headache	Study investigated 136 attacks in 16 patients reported in Broggi[2]. 79.4% (108/136) had 20 minutes of stimulation or pain resolution. Pain intensity reduction of greater than 50% occurred in 25 of 108 attacks.	Same patients reported in table 2. No new information.
Leone M, Franzini A, Broggi G et al. (2006) Hypothalmic stimulation for intractable cluster headache: long-term experience. Neurology 67: 1502.	Case series n = 16 Follow-up = 23 months	Same outcomes reported in Broggi[2] in table 2.	Same patients and outcomes reported in table 2.
Lyons MK, Dodick MD, Evidente VG (2009) Responsiveness of short-lasting unilateral neuralgiform headache with conjunctival injection and te4aring to hypothalamic deep brain stimulation. Journal of Neurosurgery 110: 279–81.	Case report n = 1 with 36-year history of medically refractory SUNCT Follow-up = 12 months	Frequency of attacks decreased from 133 per day in the month before the procedure to 45 per day in the first month, 46 per day at 6 months and 25 per day at 12 months. Side effects of long-term stimulation included erectile dysfunction.	Larger studies included in table 2.
May A, Leone M, Boecker H et al. (2006) Hypothalamic deep brain stimulation in positron emission tomography. Journal of Neuroscience 26: 3589–93.	Case series n = 10	Study to assess brain activity in patients with deep brain electrodes. All experienced improvement after stimulation was initiated, 8 were pain-free and only 2 suffered from sporadic attacks.	Updated publications from this centre have included these patients, including a study in table 2[2].

Owen SL, Green AL, Davies P et al. (2007) Connectivity of an effective hypothalamic surgical target for cluster headache. Journal of Clinical Neuroscience 14: 955–60.	Case report n = 1 with chronic cluster headache Follow-up = 8 months	No further attacks in the 8 months after surgery.	Larger studies included in table 2.
Pinsker MO, Bartsch T, Falk D et al. (2008) Failure of deep brain stimulation of the posterior inferior hypothalamus in chronic cluster headache – report of two cases and review of the literature. Zentralblatt fur Neurochirurgie 69: 76–9.	Case series n = 2 Follow-up = 12 and 3 months	Both patients showed initial pain reduction in first days but not at follow-up (12 and 3 months, respectively). Medication could not be decreased.	Patients included in a study in table 2[4].
Sprenger T, Boecker H, Tolle TR et al. (2004) Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology 62: 516–7.	Case report n = 1 with 2-year history of chronic cluster headache	Lower frequency of attacks after implantation. Patient was reported to have had an attack in the last 30 minutes of the study while the stimulator was turned off.	Larger studies included in table 2.
Vetrugno R, Pierangeli G, Leone M et al. (2007) Effect on sleep of posterior hypothalamus stimulation in cluster headache. Headache 47: 1085–90.	Case series n = 3 chronic cluster headache	Study showed affect on sleep. During treatment, nocturnal cluster headache attacks were abolished and sleep efficiency and periodic limb movements in sleep were improved.	Larger studies included in table 2.
Walcott BP, Bamber NI, Anderson DE (2009) Successful treatment of chronic paroxysmal hemicrania with posterior hypothalamic stimulation: technical case report. Neurosurgery 65: E997	Case series n = 1 with chronic paroxysmal hemicranias	Headache symptoms were alleviated with intraoperative activation No complications.	Larger studies included in table 2.

Appendix B: Related NICE guidance for deep brain stimulation for intractable trigeminal autonomic cephalalgias

Guidance	Recommendations
Interventional procedures	**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. **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.

Appendix C: Literature search for deep brain stimulation for intractable trigeminal autonomic cephalalgias

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	23/11/2010	Issue 4 of 4, October 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	23/11/2010	N/A
HTA database (CRD website)	23/11/2010	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	23/11/2010	Issue 4 of 4, October 2010
MEDLINE (Ovid)	23/11/2010	1950 to November Week 2 2010
MEDLINE In-Process (Ovid)	23/11/2010	November 17, 2010
EMBASE (Ovid)	23/11/2010	1980 to 2010 Week 45
CINAHL (NLH Search 2.0)	23/11/2010	N/A
BLIC (Dialog DataStar)	09/03/2010	N/A
Zetoc	23/11/2010	N/A
National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database	09/03/2010	None found
Current Controlled Trials *meta*Register of Controlled Trials - *m*RCT	09/03/2010	None found
Clinicaltrials.gov	09/03/2010	Evaluation of Efficacy and Safety of Deep Brain Stimulation (DBS) in Chronic and Treatment-Resistant Cluster Headache(CH) Safety Study of Deep Brain Stimulation to Manage Thalamic Pain Syndrome

Websites searched on: 09/03/2010

- National Institute for Health and Clinical Excellence (NICE)

- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – surgical (ASERNIP-S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- 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 stimul*).tw.
3	DBS.tw.
4	dbs-stn.tw.
5	Electric Stimulation Therapy/ and exp Brain/
6	neurostimulat*.tw.
7	1 or 2 or 3 or 4 or 5 or 6
8	(chronic* adj3 pain* adj3 syndrom*).tw.
9	(pain* adj3 (phantom* or post stroke* or cancer* or neuropath*)).tw.
10	CPSP.tw.
11	Pain, Postoperative/ and exp Pain, Intractable/
12	(post* adj3 (surgical* or operat*) adj3 pain*).tw.
13	(Failed Back Surgery Syndrome/ or Low Back Pain/) and exp Pain, Intractable/
14	(low* adj3 back* adj3 pain*).tw.
15	(fail* adj3 back* adj3 surger* adj3 syndrom*).tw.
16	(post trauma* adj3 pain*).tw.
17	(Migraine Disorders/ or Cluster Headache/) and exp Pain, Intractable/
18	((headach* or migrain*) adj3 (syndrom* or disord* or chronic* or clust* or intract*)).tw.

19	(atypic* adj3 fac* adj3 pain*).tw.
20	Trigeminal Neuralgia/ and exp Pain, Intractable/
21	ATN.tw.
22	((trigemin* or trifacial) adj3 neuralgi*).tw.
23	(anaesth* adj3 dolorosa).tw.
24	(neurogen* adj3 pain*).tw.
25	(thalamic adj3 pain*).tw.
26	Phantom Limb/ and exp Pain, Intractable/
27	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	7 and 27
29	Animals/ not Humans/
30	28 not 29