

# **NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

## **INTERVENTIONAL PROCEDURES PROGRAMME**

### **Interventional procedure overview of deep brain stimulation for refractory chronic pain syndromes (excluding headache)**

#### **Treating persistent pain (except headache) using deep brain stimulation**

Refractory chronic pain syndromes are characterised by pain that persists despite treatment and for longer than expected. Causes are varied and pain can occur anywhere in the body. Chronic pain can be debilitating and have a significant impact on a person's quality of life. A variety of treatments can be used depending on the cause and precise symptoms. This procedure aims to treat chronic pain that does not respond to other treatments. It involves stimulating 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 chronic pain syndromes (excluding headache)

## **Specialty societies**

- Society of British Neurological Surgeons (SBNS)
- British Pain Society.

## Description

### ***Indications and current treatment***

Chronic refractory pain syndromes frequently have an unclear aetiology and a complex natural history. The pain may be related to damage to surrounding tissues such as muscle, skin and bones (nociceptive pain) or to the nervous system itself (neuropathic or deafferentation pain). In some cases, it is of uncertain origin (for example, in multiple sclerosis).

Treatment of chronic refractory pain usually involves a multidisciplinary approach including physical, psychological, and/or pharmacological treatments. Medication is the usual treatment for chronic neuropathic pain; this includes gabapentin, lidocaine, opioid analgesics, tramadol hydrochloride, and tricyclic antidepressants.

Neurostimulatory techniques such as spinal, motor cortex, and peripheral nerve stimulation have been introduced as treatment options for patients whose condition is unresponsive to other forms of treatment.

### ***What the procedure involves***

Deep brain stimulation involves stereotactic targeting of specific anatomical sites within the brain to modulate the central processing of the pain signal and improve the patient's symptoms. Depending on the pathophysiology of the particular pain syndrome the surgeon may choose to target the internal capsule, sensory thalamus, periaqueductal grey, periventricular grey, and other anatomical sites.

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 anaesthesia and/or intravenous sedation (general anaesthesia is sometimes used). A test stimulation (or macrostimulation) is used to check for side effects. Postoperative scans are sometimes used to assess the position of the 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'.

## Literature review

### ***Rapid review of literature***

The medical literature was searched to identify studies and reviews relevant to deep brain stimulation for chronic pain syndromes (excluding headache). 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.<br>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.<br>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 chronic pain syndromes (excluding headache).                                                                                                                                                                                                                                                                                                                                                                                         |
| 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 693 patients from 3 non-randomised comparative studies<sup>1,2,3</sup>, 1 meta-analysis of case series<sup>4</sup>, and 5 case series<sup>5,6,7,8,9</sup>.

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 chronic pain syndromes (excluding headache)**

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------------------------------------------------------------------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|-------------------------------------------|------------|------------------|-------------|-----------------|-----------|-----------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Study details                                                                                                                                                                                                                                                                                         |                 | Key efficacy findings                                             |  | Key safety findings                                                                                                                                                                                                                                                                                                                                                                    | Comments |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Katayama Y (2001) <sup>1</sup>                                                                                                                                                                                                                                                                        |                 | Number of patients analysed: <b>43 (12 DBS vs 31 MCS)</b>         |  | <b>Intraprocedural pain sensation (or stimulation-induced paresthesia)</b> <table><tr><th>Location</th><th>% with patients</th></tr><tr><td>Thalamic ventralis caudalis nucleus (DBS)</td><td>50% (6/12)</td></tr><tr><td>Post-central MCS</td><td>39% (12/31)</td></tr><tr><td>Pre-central MCS</td><td>6% (2/31)</td></tr><tr><td>Pre-frontal MCS</td><td>3% (1/31)</td></tr></table> | Location | % with patients | Thalamic ventralis caudalis nucleus (DBS) | 50% (6/12) | Post-central MCS | 39% (12/31) | Pre-central MCS | 6% (2/31) | Pre-frontal MCS | 3% (1/31) | <b>Follow-up issues:</b> <ul style="list-style-type: none"><li>Not reported.</li></ul><br><b>Study design issues:</b> <ul style="list-style-type: none"><li>Retrospective.</li><li>Few details were given in the study such as patient recruitment, patient characteristics, concurrent medications, nature of stroke and follow-up.</li><li>Treatment allocation not described.</li><li>VAS scale not described.</li><li>It appears that one patient may have been treated with both DBS and MCS but this is not clear (the study stated that one patient was 'tested for both DBS and MCS').</li></ul> |  |
| Location                                                                                                                                                                                                                                                                                              | % with patients |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Thalamic ventralis caudalis nucleus (DBS)                                                                                                                                                                                                                                                             | 50% (6/12)      |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Post-central MCS                                                                                                                                                                                                                                                                                      | 39% (12/31)     |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Pre-central MCS                                                                                                                                                                                                                                                                                       | 6% (2/31)       |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Pre-frontal MCS                                                                                                                                                                                                                                                                                       | 3% (1/31)       |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| <b>Non-randomised comparative study</b>                                                                                                                                                                                                                                                               |                 | <b>Long-term pain control</b>                                     |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Japan                                                                                                                                                                                                                                                                                                 |                 | This was reported as in the 'long term' but this was not defined. |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Recruitment period: not reported                                                                                                                                                                                                                                                                      |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Study population: patients with <b>post-stroke pain</b> following unsuccessful percutaneous spinal cord stimulation                                                                                                                                                                                   |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| n = <b>43 (12 DBS vs 31 MCS)</b>                                                                                                                                                                                                                                                                      |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Age and sex: not reported                                                                                                                                                                                                                                                                             |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Patient selection criteria: not reported                                                                                                                                                                                                                                                              |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Technique: DBS of the thalamic nucleus ventralis caudalis (if patients satisfied with results of test, stimulations were internalised)                                                                                                                                                                |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Follow-up: <b>not reported</b>                                                                                                                                                                                                                                                                        |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| Conflict of interest/source of funding: supported by grant from the Japanese Ministry of Science and Culture                                                                                                                                                                                          |                 |                                                                   |  |                                                                                                                                                                                                                                                                                                                                                                                        |          |                 |                                           |            |                  |             |                 |           |                 |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                     |                                                                                          |     |             |     |              |     |              |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Study details                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Key efficacy findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Key safety findings | Comments                                                                                 |     |             |     |              |     |              |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p>Katayama Y (2001)<sup>2</sup></p> <p><b>Non-randomised comparative study</b></p> <p>Japan</p> <p>Recruitment period: not reported</p> <p>Study population: patients with <b>phantom limb pain</b> following unsuccessful percutaneous spinal cord stimulation</p> <p>n = <b>19 (10 DBS vs 5 MCS vs 4 DBS and MCS)</b></p> <p>Age and sex: not reported</p> <p>Patient selection criteria: not reported</p> <p>Technique: DBS of the thalamic nucleus ventralis caudalis (if patients satisfied with results of test, simulations were internalised)</p> <p>Follow-up: <b>2 to 18 years</b></p> <p>Conflict of interest/source of funding: supported by grant from the Japanese Ministry of Science and Culture</p> | <p>Number of patients analysed: <b>19 (10 DBS vs 5 MCS vs 4 DBS and MCS)</b></p> <p><i>Long-term pain control</i></p> <table><tr><th>Treatment</th><th>% of patients with pain reduction of greater than 80% on VAS (considered 'satisfactory')</th></tr><tr><td>SCS</td><td>32% (6/19)*</td></tr><tr><td>DBS</td><td>60% (6/10)**</td></tr><tr><td>MCS</td><td>20% (1/5)***</td></tr></table> <p>*All patients had SCS before being treated with DBS or MCS; 2 had complete pain control from SCS.</p> <p>**Of the 6 with 'satisfactory' results, 4 had pain from brachial plexus avulsion; 1 patient without 'satisfactory' results continued using DBS for partial pain control; 2 of these patients had complete pain control.</p> <p>***1 patient continued to use MCS despite partial pain control; both the patient with partial pain control and more than 80% reduction in pain had pain from brachial plexus avulsion.</p> <p>4 additional patients underwent both DBS and MCS – 1 responded better to MCS and 2 responded better to DBS (response of fourth patient not reported).</p> | Treatment           | % of patients with pain reduction of greater than 80% on VAS (considered 'satisfactory') | SCS | 32% (6/19)* | DBS | 60% (6/10)** | MCS | 20% (1/5)*** | <p>Not reported.</p> | <p><b>Follow-up issues:</b></p> <ul style="list-style-type: none"><li>Not reported</li></ul> <p><b>Study design issues:</b></p> <ul style="list-style-type: none"><li>Retrospective.</li><li>Treatment allocation not described.</li><li>VAS scale not described.</li><li>The study also reported on 4 patients who had both DBS and MCS after failed spinal cord stimulation.</li></ul> <p><b>Study population issues:</b></p> <ul style="list-style-type: none"><li>Phantom limb pain was caused by trauma, neoplasms or infections in 8 patients and after brachial plexus avulsion in 11 patients. Most of those in the later group had amputation.</li><li>Patient characteristics were not described, including any medications.</li></ul> <p><b>Study design issues:</b></p> <ul style="list-style-type: none"><li>The patient numbers in the study are not clear. It is not clear if the 6 patients with a satisfactory response to SCS (and, therefore, were not treated with DBS or MCS) are included in the total 19 patients in the study.</li></ul> |
| Treatment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | % of patients with pain reduction of greater than 80% on VAS (considered 'satisfactory')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                     |                                                                                          |     |             |     |              |     |              |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| SCS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 32% (6/19)*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                     |                                                                                          |     |             |     |              |     |              |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| DBS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 60% (6/10)**                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                                                                                          |     |             |     |              |     |              |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| MCS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 20% (1/5)***                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                                                                                          |     |             |     |              |     |              |                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                    |                                     |                                    |         |   |     |   |       |   |   |     |       |   |     |   |       |   |     |     |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Study details                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Key efficacy findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Key safety findings                | Comments                            |                                    |         |   |     |   |       |   |   |     |       |   |     |   |       |   |     |     |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>Nandi D (2002)<sup>3</sup></p> <p><b>Non-randomised comparative study</b><br/>UK</p> <p>Recruitment period: 1995 – 1999 (MCS), 2000 – 2001 (DBS)</p> <p>Study population: <b>post-stroke neuropathic pain</b><br/>n = <b>10 (4 DBS vs 6 MCS)</b></p> <p>Characteristics of patients treated with DBS: mean age 70.5 years, 66.7% male, 2 thalamic infarct, 1 sub-arachnoid haemorrhage</p> <p>Characteristics of patients treated with MCS: mean age 59.5 years, 50% male, 2 thalamic infarct, 1 occipital infarct, 1 also had trigeminal neuralgia</p> <p>Patient selection criteria: not reported</p> <p>Technique: DBS in ventroposterolateral thalamic nucleus and PVG; electrodes externalised for 1 week of trial stimulation – during this, the DBS was turned 'off' and 'on' 5 times to test the affect; if patients were satisfied with degree of pain relief, pulse generator implanted under general anaesthesia</p> <p>Follow-up: <b>6 months (DBS) and 2 week to 31 months (MCS)</b></p> <p>Conflict of interest/source of funding: study funded by Medical Research Council and Norman Collisson Foundation</p> | <p>Number of patients analysed: <b>10 (4 DBS vs 6 MCS)</b></p> <p><b>Pain relief from DBS</b></p> <p><i>During trial period:</i> 3 of 4 patients had a significant difference in VAS score between the period when the DBS was turned off and when it was turned on.</p> <p>One of the 3 patients with significant difference in VAS score did not have full implantation despite 40% decreased in VAS score (not reported why)</p> <table border="1"> <thead> <tr> <th>Patient</th><th>Mean VAS score over 5 'off' periods</th><th>Mean VAS score over 5 'on' periods</th><th>p value</th></tr> </thead> <tbody> <tr> <td>1</td><td>8.8</td><td>5</td><td>0.024</td></tr> <tr> <td>2</td><td>9</td><td>5.8</td><td>0.005</td></tr> <tr> <td>3</td><td>8.4</td><td>5</td><td>0.001</td></tr> <tr> <td>4</td><td>8.4</td><td>8.2</td><td>0.89</td></tr> </tbody> </table> <p>(using McGill-Melzack scale – see comments section)</p> <p><i>After implantation of generator:</i> Of the 2 patients with implantation of the generator, 1 had greater than 60% pain relief for 3 months and the other had 40% pain relief for 6 months.</p> <p><b>Pain relief in from MCS</b></p> <ul style="list-style-type: none"> <li>- 50% (3/6) had no pain relief</li> <li>- 1 had initial pain relief (greater than 50%) lasting 2–3 weeks. The patient died of an unrelated cause 7 months later</li> <li>- 1 had no pain for 31 months but then died from unrelated causes</li> <li>- 1 had initial pain relief of 70% lasting 2–3 weeks at time of report.</li> </ul> | Patient                            | Mean VAS score over 5 'off' periods | Mean VAS score over 5 'on' periods | p value | 1 | 8.8 | 5 | 0.024 | 2 | 9 | 5.8 | 0.005 | 3 | 8.4 | 5 | 0.001 | 4 | 8.4 | 8.2 | 0.89 | <p><b>Complications from DBS</b></p> <ul style="list-style-type: none"> <li>- 1 patient developed CSF leak when the electrode was being inserted into the PVG so the electrode was not implanted into the PVG. This patient had haematoma over the pulse generator site in the second stage (no more details provided).</li> </ul> <p><b>Complications from MCS</b></p> <ul style="list-style-type: none"> <li>- 1 patient had subdural haematoma with secondary wound infection requiring explantation of the electrode</li> <li>- 1 patient had a fit induced during postoperative titration (no pain relief despite motor response during postoperative titration)</li> <li>- 1 patient had a strong motor response elicited during intraoperative test stimulation</li> <li>- 1 patient was affected by exposure to external magnetic field (No more details provided for any of these events).</li> </ul> | <p><b>Follow-up issues:</b></p> <ul style="list-style-type: none"> <li>• Not reported.</li> </ul> <p><b>Study design issues:</b></p> <ul style="list-style-type: none"> <li>• Patient allocation not described.</li> <li>• Pain was assessed before operation and during stimulation with a self-rated analogue scale (McGill-Melzack) but this scale was not described (higher scores appear to indicate worse pain).</li> <li>• Patients responded better to the PVG stimulation than ventroposterolateral thalamic nucleus stimulation in the trial period.</li> </ul> <p><b>Study population issues:</b></p> <ul style="list-style-type: none"> <li>• Patients treated with DBS included more males and were older than those treated with MCS.</li> </ul> |
| Patient                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Mean VAS score over 5 'off' periods                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Mean VAS score over 5 'on' periods | p value                             |                                    |         |   |     |   |       |   |   |     |       |   |     |   |       |   |     |     |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 8.8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 5                                  | 0.024                               |                                    |         |   |     |   |       |   |   |     |       |   |     |   |       |   |     |     |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 5.8                                | 0.005                               |                                    |         |   |     |   |       |   |   |     |       |   |     |   |       |   |     |     |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 8.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 5                                  | 0.001                               |                                    |         |   |     |   |       |   |   |     |       |   |     |   |       |   |     |     |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 8.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 8.2                                | 0.89                                |                                    |         |   |     |   |       |   |   |     |       |   |     |   |       |   |     |     |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Study details                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                | Key efficacy findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | Key safety findings | Comments     |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>Bittar RG (2005)<sup>4</sup></p> <p><b>Meta-analysis</b></p> <p>UK, Australia</p> <p>Recruitment period: search from 1966 to 2003</p> <p>Study population: studies with patients treated with DBS for intractable pain with known origin with clearly described protocol</p> <p><b>n = 424 cases from 6 case series published between 1977 and 1997</b></p> <p>Age: not reported</p> <p>Sex: not reported</p> <p>Exclusion criteria: studies with patients that have neuroses/psychoses and severe depression</p> <p>Technique: pre-operatively neuroimaging followed by implantation of electrodes in PVG, PAG, IC or ST (some studies used implants in several places); DBS with varying amplitudes depending on location of implant (from 1 to 8 V with 0.1 to 0.8 ms, from 5 to 100 Hz); internalisation of stimulation system only performed when patients reported a favorable outcome after test period</p> <p>Follow-up: <b>from 1 month to 15 years</b></p> <p>Conflict of interest/source of funding: not reported</p> |                                | <p>Number of patients analysed: <b>424 cases from 6 studies</b></p> <p><b>Pain relief</b></p> <p>Definition of success and failure varied between the studies so was given as reported in the study</p> <table><tr><th>Type of pain</th><th>Success rate</th><th>p value</th></tr><tr><td>Nociceptive vs deafferentation*</td><td>63% (129/204) vs 47% (103/220)</td><td>&lt; 0.01</td></tr><tr><td>Central vs peripheral deafferentation pain</td><td>31% (14/45) vs 51% (89/175)</td><td>&lt; 0.03</td></tr></table> <p><i>By site of stimulation:</i></p> <table><tr><td>PAG/PVG</td><td>79.1% (117/148)</td><td rowspan="4">&lt; 0.05**</td></tr><tr><td>PAG/PVG + ST/IC</td><td>87.3% (48/55)</td></tr><tr><td>ST</td><td>58.0% (58/100)</td></tr><tr><td>ST or IC</td><td>37.5% (6/16)</td></tr></table> <p>* This includes patients treated with both central and peripheral deafferentation pain.</p> <p>**Between ST alone and PAG/PVG ± ST.</p> <p><b>Rate of long-term success by aetiology of pain among the studies</b></p> <table><tr><th>Aetiology of pain</th><th colspan="2">% with success</th></tr><tr><td></td><th>With chronic stimulation</th><th>Of cases internalised*</th></tr><tr><td>Thalamic (central lesion)</td><td>31.1% (14/45)</td><td>58.3%</td></tr><tr><td>Phantom limb and stump</td><td>44.4% (4/9)</td><td>57.1%</td></tr><tr><td>Cervical root and/or brachial plexus lesion</td><td>50.0% (6/12)</td><td>66.7%</td></tr><tr><td>Failed back syndrome</td><td>78.0%</td><td>85.2%</td></tr></table> |  | Type of pain        | Success rate | p value | Nociceptive vs deafferentation* | 63% (129/204) vs 47% (103/220) | < 0.01 | Central vs peripheral deafferentation pain | 31% (14/45) vs 51% (89/175) | < 0.03 | PAG/PVG | 79.1% (117/148) | < 0.05** | PAG/PVG + ST/IC | 87.3% (48/55) | ST | 58.0% (58/100) | ST or IC | 37.5% (6/16) | Aetiology of pain | % with success |  |  | With chronic stimulation | Of cases internalised* | Thalamic (central lesion) | 31.1% (14/45) | 58.3% | Phantom limb and stump | 44.4% (4/9) | 57.1% | Cervical root and/or brachial plexus lesion | 50.0% (6/12) | 66.7% | Failed back syndrome | 78.0% | 85.2% | Not reported | <p><b>Follow-up issues:</b></p> <ul style="list-style-type: none"><li>• Not reported.</li></ul> <p><b>Study design issues:</b></p> <ul style="list-style-type: none"><li>• Studies from MEDLINE or EMBASE.</li><li>• Of 12 studies identified, 6 fit inclusion criteria.</li><li>• Neuropathic pain generally treated bilaterally in PAG/PVG and non-neuropathic generally treated in contralateral ST.</li><li>• Technology of the generators used changed throughout the course of the study.</li><li>• Preoperative neuroimaging with contrast/air ventriculography intraoperatively in the older studies and with CT or MRI preoperatively in the later studies.</li><li>• Methods to evaluate pain were inconsistent. Pain relief evaluation was usually carried out by physician not involved in implantation.</li><li>• Terminology was ambiguous and inconsistent. 'Central' pain was restricted to only include thalamic or</li></ul> |
| Type of pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Success rate                   | p value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Nociceptive vs deafferentation*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 63% (129/204) vs 47% (103/220) | < 0.01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Central vs peripheral deafferentation pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 31% (14/45) vs 51% (89/175)    | < 0.03                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| PAG/PVG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 79.1% (117/148)                | < 0.05**                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| PAG/PVG + ST/IC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 87.3% (48/55)                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| ST                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 58.0% (58/100)                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| ST or IC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 37.5% (6/16)                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Aetiology of pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | % with success                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | With chronic stimulation       | Of cases internalised*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Thalamic (central lesion)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 31.1% (14/45)                  | 58.3%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Phantom limb and stump                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 44.4% (4/9)                    | 57.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Cervical root and/or brachial plexus lesion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 50.0% (6/12)                   | 66.7%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Failed back syndrome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 78.0%                          | 85.2%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                     |              |         |                                 |                                |        |                                            |                             |        |         |                 |          |                 |               |    |                |          |              |                   |                |  |  |                          |                        |                           |               |       |                        |             |       |                                             |              |       |                      |       |       |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale

| Study details | Key efficacy findings               |                 |       | Key safety findings | Comments                                                                          |
|---------------|-------------------------------------|-----------------|-------|---------------------|-----------------------------------------------------------------------------------|
|               |                                     | (46/59)         |       |                     | suprathalamic lesions.                                                            |
|               | Peripheral neuropathy/radiculopathy | 52.2% (12/23)   | 75.0% |                     | • Details of statistical tests used not reported.                                 |
|               | Trigeminal neuropathy               | 100% (4/4)      | 100%  |                     | <b>Study population issues:</b>                                                   |
|               | Post-herpetic neuralgia             | 36.4% (4/11)    | 66.7% |                     | • Various aetiologies of pain (see efficacy).                                     |
|               | Causalgia                           | 80.0% (4/5)     | 80.0% |                     | <b>Other issues:</b>                                                              |
|               | Cancer                              | 65.2% (15/23)   | 78.9% |                     | • Some studies did preoperative psychiatric evaluation and pharmacological tests. |
|               | Anaesthesia dolorosa                | 28.6% (8/28)    | 47.1% |                     |                                                                                   |
|               | Paraplegia/paraparesis/quadriplegia | 10.0% (2/20)    | 28.6% |                     |                                                                                   |
|               | Post-cordotomy dysesthesia          | 71.4% (10/14)   | 90.9% |                     |                                                                                   |
|               | Lumbosacral radiculopathy           | 90.5% (19/21)   | 95.0% |                     |                                                                                   |
|               | Cauda equine syndrome               | 100% (3/3)      | 100%  |                     |                                                                                   |
|               | Low back and skeletal               | 54.4% (56/103)  | 80.0% |                     |                                                                                   |
|               | Thoracic neuralgia                  | 25.0% (1/4)     | 33.3% |                     |                                                                                   |
|               | Miscellaneous neuropathic           | 66.7% (4/6)     | 100%  |                     |                                                                                   |
|               | Atypical facial                     | 100% (1/1)      | 100%  |                     |                                                                                   |
|               | Osteoporosis                        | 0% (0/1)        | 0%    |                     |                                                                                   |
|               | Spinal cord injury                  | 50.0% (5/10)    | 71.4% |                     |                                                                                   |
|               | Postoperative/traumatic pain        | 55.6% (5/9)     | 55.6% |                     |                                                                                   |
|               | Glossodynia                         | 0% (0/1)        | 0%    |                     |                                                                                   |
|               | Non-malignant                       | 33.3% (1/3)     | 33.3% |                     |                                                                                   |
|               | Lumbar archnoiditis                 | 77.8% (7/9)     | 87.5% |                     |                                                                                   |
|               | Total                               | 54.7% (232/424) | 76.1% |                     |                                                                                   |
|               | *Absolute figures not reported.     |                 |       |                     |                                                                                   |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                     |                                                                           |                                  |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
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| Study details                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                     | Key efficacy findings                                                     |                                  |                                     | Key safety findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                  | Comments                 |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| <p>Levy RM (1987)<sup>5</sup></p> <p><b>Case series (included in metaanalysis above<sup>4</sup>)</b></p> <p>USA</p> <p>Recruitment period: 1972 – 1984</p> <p>Study population: patients with <b>severe, chronic, intractable pain</b> that have failed other available medical and surgical therapies</p> <p><b>n = 141 (84 with deafferentation pain and 57 with nociceptive pain)</b></p> <p>Mean age: 51.2 years</p> <p>Sex: roughly equal for deafferentation pain (but more women with facial anaesthesia and more men with phantom limb pain)</p> <p>Average time with severe pain: 65 months</p> <p>Patient selection criteria: patients who had exhausted other medical and surgical therapies</p> <p>Exclusion criteria: gross psychiatric illness or with intellectual handicaps</p> <p>Technique: electrode implantation in nucleus ventralis posterolateralis or PVG/PAG (some bilateral) under local anaesthesia, test stimulation with externalised electrode lead, if pain relief after 1 to several days, electrodes may be implanted subcutaneously over the</p>                                                                                                                                                                                                                                                                                                                                                                     |                                     | Number of patients analysed: <b>141 (57 with nociceptive pain)</b>        |                                  |                                     | <p><b>Major complications</b></p> <table><tr><th>Complication</th><th>Frequency</th></tr><tr><td>Intracranial haemorrhage (intracerebral 3, epidural 1, periventricular 1)</td><td>3.5% (5/141)<sup>a</sup></td></tr><tr><td>Infection, largely superficial, skin apart from 1 with meningitis</td><td>12.1% (17/141)<sup>b</sup></td></tr><tr><td>Erosion of hardware</td><td>7.1% (10/141)<sup>c</sup></td></tr><tr><td>Foreign body reaction (requiring DBS system removal in 4)</td><td>5.0% (7/141)</td></tr><tr><td>Psychosis (2 with history of drug abuse)</td><td>2.1% (3/141)</td></tr><tr><td>Electrode migration resulting in failure</td><td>9.9% (14/141)<sup>d</sup></td></tr><tr><td>Leakage of current into soft tissues</td><td>8.5% (12/141)<sup>e</sup></td></tr><tr><td>Other hardware failure</td><td>4.3% (6/141)<sup>f</sup></td></tr></table> <p><sup>a</sup>1 patient with intracerebral haemorrhage died, 2 were left with significant neurological deficits and in 2 patients the deficit was completely resolved; <sup>b</sup>23 cases occurred in 17 patients; 12 within 30 days and 10 thereafter (occurrence of 1 not reported); successfully treated with antibiotics alone (n = 1), antibiotic and local debridement (n = 2), antibiotics and electrode removal successful (n = 11) (not clear about other 3 patients); <sup>c</sup> without infection: 5 had the non-functioning system removed and 5 had re-implantation without antibiotic therapy and without further complication; <sup>d</sup>20 times in 14 patients (early designs only); <sup>e</sup> usually from electrical</p> |                                  | Complication             | Frequency     | Intracranial haemorrhage (intracerebral 3, epidural 1, periventricular 1) | 3.5% (5/141) <sup>a</sup> | Infection, largely superficial, skin apart from 1 with meningitis | 12.1% (17/141) <sup>b</sup> | Erosion of hardware   | 7.1% (10/141) <sup>c</sup> | Foreign body reaction (requiring DBS system removal in 4) | 5.0% (7/141) | Psychosis (2 with history of drug abuse) | 2.1% (3/141)         | Electrode migration resulting in failure | 9.9% (14/141) <sup>d</sup> | Leakage of current into soft tissues | 8.5% (12/141) <sup>e</sup> | Other hardware failure | 4.3% (6/141) <sup>f</sup> | <b>Follow-up issues:</b> |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Complication                                                              | Frequency                        |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Intracranial haemorrhage (intracerebral 3, epidural 1, periventricular 1) | 3.5% (5/141) <sup>a</sup>        |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Infection, largely superficial, skin apart from 1 with meningitis         | 12.1% (17/141) <sup>b</sup>      |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Erosion of hardware                                                       | 7.1% (10/141) <sup>c</sup>       |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Foreign body reaction (requiring DBS system removal in 4)                 | 5.0% (7/141)                     |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Psychosis (2 with history of drug abuse)                                  | 2.1% (3/141)                     |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Electrode migration resulting in failure                                  | 9.9% (14/141) <sup>d</sup>       |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Leakage of current into soft tissues                                      | 8.5% (12/141) <sup>e</sup>       |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     | Other hardware failure                                                    | 4.3% (6/141) <sup>f</sup>        |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| <p><b>Pain relief for deafferentation pain (n = 84)</b></p> <table><tr><th>Aetiology</th><th>Preoperative pain duration (months)</th><th>Mean no. of previous operations</th><th>% with initial success (6 weeks)</th><th>% with long-term success</th></tr><tr><td>Thalamic pain</td><td>39.8</td><td>0</td><td>56% (14/25)</td><td>24% (6/25)</td></tr><tr><td>Peripheral neuropathy</td><td>71.1</td><td>3.9</td><td>69% (11/16)</td><td>50% (8/16)</td></tr><tr><td>Anaesthesia dolorosa</td><td>102.9</td><td>2.8</td><td>67% (8/12)</td><td>18% (2/?)<sup>**</sup></td></tr><tr><td>Paraplegia pain</td><td>95.9</td><td>2.3</td><td>36% (4/11)</td><td>0%</td></tr><tr><td>Postcordotomy dysesthesia</td><td>100.6</td><td>0.4</td><td>60% (3/5)</td><td>50% (2/?)<sup>**</sup></td></tr><tr><td>Phantom limb</td><td>142.6</td><td>2.2</td><td>80% (4/5)</td><td>20% (1/5)</td></tr><tr><td>Thoracic neuralgia</td><td>49.8</td><td>2.5</td><td>75% (3/4)</td><td>25% (1/4)</td></tr><tr><td>Miscellaneous*</td><td>87.7</td><td>2.8</td><td>67% (4/6)</td><td>67% (4/6)</td></tr><tr><td>Total</td><td>59.3</td><td>1.9</td><td>61% (51/84)</td><td>30% (24/?)<sup>**</sup></td></tr></table> <p>*Including atypical facial pain (2), post-herpetic neuralgia (1), brachial plexus avulsion (1), deafferentation perineal pain (1), extremity pain secondary to Friedrich's ataxia.</p> <p><sup>**</sup>denominators not clear from study</p> |                                     |                                                                           | Aetiology                        | Preoperative pain duration (months) | Mean no. of previous operations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | % with initial success (6 weeks) | % with long-term success | Thalamic pain | 39.8                                                                      | 0                         | 56% (14/25)                                                       | 24% (6/25)                  | Peripheral neuropathy | 71.1                       | 3.9                                                       | 69% (11/16)  | 50% (8/16)                               | Anaesthesia dolorosa | 102.9                                    | 2.8                        | 67% (8/12)                           | 18% (2/?) <sup>**</sup>    | Paraplegia pain        | 95.9                      | 2.3                      | 36% (4/11) | 0% | Postcordotomy dysesthesia | 100.6 | 0.4 | 60% (3/5) | 50% (2/?) <sup>**</sup> | Phantom limb | 142.6 | 2.2 | 80% (4/5) | 20% (1/5) | Thoracic neuralgia | 49.8 | 2.5 | 75% (3/4) | 25% (1/4) | Miscellaneous* | 87.7 | 2.8 | 67% (4/6) | 67% (4/6) | Total | 59.3 | 1.9 | 61% (51/84) | 30% (24/?) <sup>**</sup> |
| Aetiology                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Preoperative pain duration (months) | Mean no. of previous operations                                           | % with initial success (6 weeks) | % with long-term success            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Thalamic pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 39.8                                | 0                                                                         | 56% (14/25)                      | 24% (6/25)                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Peripheral neuropathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 71.1                                | 3.9                                                                       | 69% (11/16)                      | 50% (8/16)                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Anaesthesia dolorosa                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 102.9                               | 2.8                                                                       | 67% (8/12)                       | 18% (2/?) <sup>**</sup>             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Paraplegia pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 95.9                                | 2.3                                                                       | 36% (4/11)                       | 0%                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Postcordotomy dysesthesia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 100.6                               | 0.4                                                                       | 60% (3/5)                        | 50% (2/?) <sup>**</sup>             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Phantom limb                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 142.6                               | 2.2                                                                       | 80% (4/5)                        | 20% (1/5)                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Thoracic neuralgia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 49.8                                | 2.5                                                                       | 75% (3/4)                        | 25% (1/4)                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Miscellaneous*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 87.7                                | 2.8                                                                       | 67% (4/6)                        | 67% (4/6)                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |
| Total                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 59.3                                | 1.9                                                                       | 61% (51/84)                      | 30% (24/?) <sup>**</sup>            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |                          |               |                                                                           |                           |                                                                   |                             |                       |                            |                                                           |              |                                          |                      |                                          |                            |                                      |                            |                        |                           |                          |            |    |                           |       |     |           |                         |              |       |     |           |           |                    |      |     |           |           |                |      |     |           |           |       |      |     |             |                          |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Study details                                                                                                                                                                                                                                                                                         |                                      | Key efficacy findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                         |                           | Key safety findings |                                      | Comments                          |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| chest wall<br><br>Mean follow-up: <b>80 months (6.8 years)</b><br><br>Conflict of interest/source of funding: first author supported with research fellowship from American Association of Neurological Surgeons                                                                                      |                                      | <b>Pain relief for patient of nociceptive pain (n = 57)</b> <table><tr><th>Aetiolog y</th><th>Preoper ative pain duration (months)</th><th>Mean no. of previ ous opera tions</th><th>% with initial succes s</th><th>% with long-term succes s</th></tr><tr><td>Cancer pain</td><td>35.5</td><td>0.8</td><td>50% (3/6)</td><td>33% (2/6)</td></tr><tr><td>Low back and skeletal pain*</td><td>153.6</td><td>4.4**</td><td>57% (29/51)</td><td>32% (16/?) ***</td></tr><tr><td>Total</td><td>141.1</td><td>4.1</td><td>56% (32/57)</td><td>32% (18/57)</td></tr></table> <p>*This included 'failed low back' syndrome.<br/>**These included repeat laminectomy, fusion and scar resection, and attempts at spinal dorsal column stimulation.<br/>***denominator not clear from study</p> |                         |                           | Aetiolog y          | Preoper ative pain duration (months) | Mean no. of previ ous opera tions | % with initial succes s | % with long-term succes s | Cancer pain | 35.5 | 0.8 | 50% (3/6) | 33% (2/6) | Low back and skeletal pain* | 153.6 | 4.4** | 57% (29/51) | 32% (16/?) *** | Total | 141.1 | 4.1 | 56% (32/57) | 32% (18/57) | insulation fractures; <sup>†</sup> corrected by replacement of specific components.<br><b>Minor complications</b> (undetected by patients, considered insignificant by the physician or had resolved by discharge from the hospital) <table><tr><th>Complication</th><th>Frequency</th></tr><tr><td>Headache*</td><td>51% (72/141)</td></tr><tr><td>Diplopia**</td><td>14.2% (20/141)</td></tr><tr><td>Nausea**</td><td>10.6% (15/141)</td></tr><tr><td>Vertical gaze palsies**</td><td>9.9% (14/141)</td></tr><tr><td>Blurred vision**</td><td>9.2% (13/141)</td></tr><tr><td>Horizontal nystagmus**</td><td>4.3% (6/141)</td></tr><tr><td>Persistent oscillopsia**</td><td>3.5% (5/141)</td></tr><tr><td>Hemi- or monoparesis</td><td>8.5% (12/141)</td></tr><tr><td>Confusion</td><td>7.8% (11/141)</td></tr><tr><td>Lethargy</td><td>6.4% (9/141)</td></tr><tr><td>Dysphasia</td><td>5.7% (8/141)</td></tr><tr><td>Local pain</td><td>5.0% (7/141)</td></tr></table> <p>*Most were transient but 8 persisted and needed further analgesic therapy, **caused by air/contrast ventriculography and PAG/PVG stimulation (all numerators calculated by analyst).The following occurred in less than 5% of patients: seizures, urinary incontinence, cranial nerve palsies, ptosis, urinary retention, bronchospasm, hypesthesia, hallucinations, photophobia, memory loss, hypotension, facial pain, hypertension, shortness of breath, dysphoria, thrombophlebitis, and stimulation-induced sleep.</p> |  | Complication | Frequency | Headache* | 51% (72/141) | Diplopia** | 14.2% (20/141) | Nausea** | 10.6% (15/141) | Vertical gaze palsies** | 9.9% (14/141) | Blurred vision** | 9.2% (13/141) | Horizontal nystagmus** | 4.3% (6/141) | Persistent oscillopsia** | 3.5% (5/141) | Hemi- or monoparesis | 8.5% (12/141) | Confusion | 7.8% (11/141) | Lethargy | 6.4% (9/141) | Dysphasia | 5.7% (8/141) | Local pain | 5.0% (7/141) | eradicated by advances in the design of the hardware. <ul style="list-style-type: none"><li>• Patient recruitment not described.</li></ul> <b>Study population issues:</b> <ul style="list-style-type: none"><li>• Various aetiologies of pain (see efficacy)</li></ul> <b>Other issues:</b> <ul style="list-style-type: none"><li>• Preoperative test included morphine and intravenous fusion and provocative naloxone testing but these were not consistently used in the study period.</li></ul> |
| Aetiolog y                                                                                                                                                                                                                                                                                            | Preoper ative pain duration (months) | Mean no. of previ ous opera tions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | % with initial succes s | % with long-term succes s |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Cancer pain                                                                                                                                                                                                                                                                                           | 35.5                                 | 0.8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 50% (3/6)               | 33% (2/6)                 |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Low back and skeletal pain*                                                                                                                                                                                                                                                                           | 153.6                                | 4.4**                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 57% (29/51)             | 32% (16/?) ***            |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Total                                                                                                                                                                                                                                                                                                 | 141.1                                | 4.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 56% (32/57)             | 32% (18/57)               |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Complication                                                                                                                                                                                                                                                                                          | Frequency                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Headache*                                                                                                                                                                                                                                                                                             | 51% (72/141)                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Diplopia**                                                                                                                                                                                                                                                                                            | 14.2% (20/141)                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Nausea**                                                                                                                                                                                                                                                                                              | 10.6% (15/141)                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Vertical gaze palsies**                                                                                                                                                                                                                                                                               | 9.9% (14/141)                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Blurred vision**                                                                                                                                                                                                                                                                                      | 9.2% (13/141)                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Horizontal nystagmus**                                                                                                                                                                                                                                                                                | 4.3% (6/141)                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Persistent oscillopsia**                                                                                                                                                                                                                                                                              | 3.5% (5/141)                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Hemi- or monoparesis                                                                                                                                                                                                                                                                                  | 8.5% (12/141)                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Confusion                                                                                                                                                                                                                                                                                             | 7.8% (11/141)                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Lethargy                                                                                                                                                                                                                                                                                              | 6.4% (9/141)                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Dysphasia                                                                                                                                                                                                                                                                                             | 5.7% (8/141)                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Local pain                                                                                                                                                                                                                                                                                            | 5.0% (7/141)                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                           |                     |                                      |                                   |                         |                           |             |      |     |           |           |                             |       |       |             |                |       |       |     |             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |              |           |           |              |            |                |          |                |                         |               |                  |               |                        |              |                          |              |                      |               |           |               |          |              |           |              |            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  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| Study details                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Key efficacy findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |           |         | Key safety findings | Comments    |           |         |               |    |   |   |                 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| <div>Hosobuchi Y (1986)<sup>8</sup></div> <div>Case series (included in meta-analysis above<sup>4</sup>)</div> <div>USA</div> <div>Recruitment period: 1970–1982</div> <div>Study population: patients with <b>severe, chronic, intractable pain</b> refractory to treatment</div> <div>n = <b>122 (76 for deafferentation pain and 65 for pain of peripheral origin)</b></div> <div>Mean age: 50 years</div> <div>Sex: 45% male</div> <div>Average time with severe pain: 6.5 years</div> <div>Patient selection criteria: patients who had exhausted other medical and surgical therapies and had a physiological condition known to be associated with pain</div> <div>Exclusion criteria: inability to control self-stimulation device, obvious psychological or psychiatric disorder</div> <div>Technique: electrode implantation PAG; ventral posterior medialis (bilateral) or ST under local anaesthesia; test stimulation with externalised electrode lead; if pain relief after 1 to several days, electrodes may be implanted subcutaneously over the chest wall; controlled by patient</div> <div>Mean follow-up: <b>2 to 14 years</b></div> <div>Conflict of interest/source of funding: Medtronic</div> | <div>Number of patients analysed: <b>122</b></div> <div>Therapy was considered a ‘success’ if the patient was able to control the pain with the electrode alone or together with medication. ‘Failure’ occurred if a patient needed a narcotic at any time during the follow-up period or if complication caused death.</div> <div>Pain relief in <u>trial stimulation</u> of subcortical ST region for deafferentation pain (n = 76)</div> <table><tr><th>Aetiology</th><th>No of cases</th><th>Successes</th><th>Failure</th></tr><tr><td>Thalamic pain</td><td>13</td><td>8</td><td>5</td></tr><tr><td>Anaesthesia dolorosa</td><td>12</td><td>5*</td><td>7</td></tr><tr><td>Post-herpetic neuralgia</td><td>5</td><td>3</td><td>2</td></tr><tr><td>Brachial plexus lesion</td><td>6</td><td>4</td><td>2</td></tr><tr><td>Paraplegia</td><td>8</td><td>3</td><td>5</td></tr><tr><td>Phantom limb pain</td><td>2</td><td>1</td><td>1</td></tr><tr><td>Postcordotomy dysesthesia</td><td>9</td><td>8</td><td>1</td></tr><tr><td>Lumbosacral radiculopathy</td><td>21</td><td>20</td><td>1</td></tr><tr><td>Total</td><td>76</td><td>52</td><td>54</td></tr></table> <div>*1 had total or almost complete relief in less than 6 months of stimulation</div> <div>Pain relief after <u>permanent stimulation</u> of subcortical ST region for deafferentation pain (n = 52)</div> <table><tr><th>Aetiology</th><th>No of cases</th><th>Successes</th><th>Failure</th></tr><tr><td>Thalamic pain</td><td>8</td><td>6</td><td>2</td></tr><tr><td>Anaesthesia dolorosa</td><td>5</td><td>4</td><td>1</td></tr><tr><td>Post-herpetic neuralgia</td><td>3</td><td>2*</td><td>1</td></tr><tr><td>Brachial plexus lesion</td><td>4</td><td>2*</td><td>2</td></tr></table> |           |         | Aetiology           | No of cases | Successes | Failure | Thalamic pain | 13 | 8 | 5 | Anaesthesia dolorosa | 12 | 5* | 7 | Post-herpetic neuralgia | 5 | 3 | 2 | Brachial plexus lesion | 6 | 4 | 2 | Paraplegia | 8 | 3 | 5 | Phantom limb pain | 2 | 1 | 1 | Postcordotomy dysesthesia | 9 | 8 | 1 | Lumbosacral radiculopathy | 21 | 20 | 1 | Total | 76 | 52 | 54 | Aetiology | No of cases | Successes | Failure | Thalamic pain | 8 | 6 | 2 | Anaesthesia dolorosa | 5 | 4 | 1 | Post-herpetic neuralgia | 3 | 2* | 1 | Brachial plexus lesion | 4 | 2* | 2 | <div>Complications</div> <table><tr><th>Complication</th><th>Frequency</th></tr><tr><td>Intracerebral haemorrhage</td><td>1.6% (2/122;1 death)<sup>a</sup></td></tr><tr><td>Ventricular haemorrhage</td><td>2.5% (3/122;1 death)<sup>b</sup></td></tr><tr><td>Ventriculitis (<i>Propionibacterium acnes</i>)</td><td>0.8% (1/122)<sup>c</sup></td></tr><tr><td>Subgaleal infection</td><td>3.3% (4/122)<sup>d</sup></td></tr><tr><td>Subdural empyema (<i>Staphylococcus aureus</i>)</td><td>0.8% (1/122)<sup>d</sup></td></tr><tr><td>Permanent eye movement dysfunction</td><td>2.5% (3/122)<sup>e</sup></td></tr><tr><td>Electrode migration resulting in no pain relief (but sequelae not described)</td><td>1.6% (2/122)</td></tr><tr><td>Erosion of the scalp overlying the connector at 1 and 1.5 years requiring plastic repair of scalp</td><td>1.6% (2/122)</td></tr></table> <div><sup>a</sup> Detected within 6 hours with CT scan; 1 patient recovered but 1 patient died from a massive cerebral oedema and haematoma in basal ganglia.</div> <div><sup>b</sup> 2 patients were successfully managed with saline solution irrigation with the patient semi-sitting; 1 had bleeding cessation on the 3<sup>rd</sup> day, had continuous ventricular drainage, and a ventriculoperitoneal shunt; the patient died</div> | Complication | Frequency | Intracerebral haemorrhage | 1.6% (2/122;1 death) <sup>a</sup> | Ventricular haemorrhage | 2.5% (3/122;1 death) <sup>b</sup> | Ventriculitis ( <i>Propionibacterium acnes</i> ) | 0.8% (1/122) <sup>c</sup> | Subgaleal infection | 3.3% (4/122) <sup>d</sup> | Subdural empyema ( <i>Staphylococcus aureus</i> ) | 0.8% (1/122) <sup>d</sup> | Permanent eye movement dysfunction | 2.5% (3/122) <sup>e</sup> | Electrode migration resulting in no pain relief (but sequelae not described) | 1.6% (2/122) | Erosion of the scalp overlying the connector at 1 and 1.5 years requiring plastic repair of scalp | 1.6% (2/122) | <div>Follow-up issues:</div> <ul style="list-style-type: none"><li>None lost in follow-up.</li></ul> <div>Study design issues:</div> <ul style="list-style-type: none"><li>Nociceptive pain treated with stimulation of PAG/PVG and differentiation of ST (36 patients had both areas stimulated; 19 with low-back pain or leg pain and 17 with deafferentation pain).</li><li>Definition of success did not include functional state.</li><li>Patient recruitment not described.</li></ul> <div>Study population issues:</div> <ul style="list-style-type: none"><li>Various aetiologies of pain (see efficacy).</li></ul> <div>Other issues:</div> |
| Aetiology                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| Complication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Frequency                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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          |                                                   |                           |                                    |                           |                                                                              |              |                                                                                                   |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Intracerebral haemorrhage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.6% (2/122;1 death) <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |           |         |                     |             |           |         |               |    |   |   |                 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| Ventricular haemorrhage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 2.5% (3/122;1 death) <sup>b</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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          |                                                   |                           |                                    |                           |                                                                              |              |                                                                                                   |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Ventriculitis ( <i>Propionibacterium acnes</i> )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.8% (1/122) <sup>c</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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          |                                                   |                           |                                    |                           |                                                                              |              |                                                                                                   |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Subgaleal infection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 3.3% (4/122) <sup>d</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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          |                                                   |                           |                                    |                           |                                                                              |              |                                                                                                   |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Subdural empyema ( <i>Staphylococcus aureus</i> )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.8% (1/122) <sup>d</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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          |                                                   |                           |                                    |                           |                                                                              |              |                                                                                                   |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Permanent eye movement dysfunction                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 2.5% (3/122) <sup>e</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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          |                                                   |                           |                                    |                           |                                                                              |              |                                                                                                   |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Electrode migration resulting in no pain relief (but sequelae not described)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 1.6% (2/122)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| Erosion of the scalp overlying the connector at 1 and 1.5 years requiring plastic repair of scalp                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1.6% (2/122)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale |                                                                                                                    |                       |                    |                 |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
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| Study details                                                                                                                                                                                                                                                                                         |                                                                                                                    | Key efficacy findings |                    |                 |                 | Key safety findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                        | Comments |
| provided technical support for the paper                                                                                                                                                                                                                                                              | Paraplegia                                                                                                         |                       | 3                  | 2               | 1               | suddenly 9 weeks later from massive coronary occlusion.<br><sup>c</sup> Ventriculitis and 3 patients with subgaleal infection successfully treated with antibiotics.<br><sup>d</sup> In 1 patient with subgaleal infection and 1 patient with subdural empyema, removal of the system hardware was required.<br><sup>e</sup> Thought to be caused by the tip of electrode being placed at the iter of the aqueduct of Sylvius and thought to be avoided by placing the electrode a few millimeters caudally. | • Preoperative test included psychological and psychiatric tests and morphine testing. |          |
|                                                                                                                                                                                                                                                                                                       | Phantom limb pain                                                                                                  |                       | 1                  | 1*              | 0               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Postcordotomy dysesthesia                                                                                          |                       | 8                  | 8*              | 0               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Lumbosacral radiculopathy                                                                                          |                       | 20                 | 19              | 1               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Total                                                                                                              |                       | 52                 | 44**            | 8               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | *1in each group had total or almost complete relief in less than 6 months of stimulation (but 3 with dysesthesia). |                       |                    |                 |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | **Pain-free for longer than 2 years.                                                                               |                       |                    |                 |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | <b><i>Pain relief in patients treated by PAG stimulation for peripheral pain (n = 65)</i></b>                      |                       |                    |                 |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | <b>Aetiology</b>                                                                                                   |                       | <b>No of cases</b> | <b>Succes s</b> | <b>Failur e</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Cancer                                                                                                             |                       | 7                  | 5               | 2               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Chronic low-back and leg pain (with herniated disc)                                                                |                       | 49*                | 39              | 7               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Peripheral neuropathy                                                                                              |                       | 1                  | 1               | 0               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Cauda equine syndrome                                                                                              |                       | 3                  | 3               | 0               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Nonmalignant abdominal pain (chronic pancreatitis)                                                                 |                       | 2                  | 1               | 1               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
|                                                                                                                                                                                                                                                                                                       | Nonmalignant perineal pain                                                                                         |                       | 1                  | 0               | 1               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
| Osteoporosis of spine                                                                                                                                                                                                                                                                                 |                                                                                                                    | 1                     | 0                  | 1               |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
| Atypical facial pain                                                                                                                                                                                                                                                                                  |                                                                                                                    | 1                     | 1                  | 0               |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
| Total                                                                                                                                                                                                                                                                                                 |                                                                                                                    | 65                    | 50                 | 12              |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |
| *19 of these had an electrode also implanted into the ST; pain was controlled more effectively with ST stimulation (all but 1 had subcutaneous implantation).                                                                                                                                         |                                                                                                                    |                       |                    |                 |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                        |          |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                         |                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
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| Study details                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Key efficacy findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                         |                         | Key safety findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| <p>Siegfried J (1987)<sup>b</sup></p> <p><b>Case series</b></p> <p>Switzerland</p> <p>Recruitment period: 1978–1985</p> <p>Study population: patients with <b>chronic intractable deafferentation pain</b> refractory to epidural dorsal cord or spinal root stimulation<br/>n = <b>112</b></p> <p>Age and sex: not reported</p> <p>Patient selection criteria: not reported</p> <p>Technique: localisation with air ventriculography or CT; implantation of thalamic sensory nucleus under local anaesthetic; test stimulation for 3–7 days; if stimulation has greatly reduced pain, subclavicular receiver or programmable implanted system under local and methohexital anaesthesia (parameters on last visit: 1.6 V, 54.52 Hz, 59.92 minutes per day for external receiver and 1.86 V, 42.72 Hz, 20.0 sec 'on' then 6.38 min 'off' for programmable implanted system)</p> <p>Follow-up: <b>6 months to 6 years</b></p> <p>Conflict of interest/source of funding: not reported</p> | <p>Number of patients analysed: <b>89 of patients who had significant pain reduction after the test stimulation and received a permanent subcutaneous receiver</b></p> <p><b>Pain relief at follow-up (6 months to 6 years)</b></p> <p>'Excellent' results were pain-free, analgesic-free, recovery to normal daily activities compatible with their neurological ability; and level '0' on a 5-grade scale of pain (5 indicating worst pain); 'improved' results were level 1 to 2 on the 5-grade pain scale; and 'failure' was 3 or 4 on the pain scale.</p> <table> <tr> <th>Aetiology</th><th>No. of cases</th><th>Excellent</th><th>Improved</th><th>Failure</th></tr> <tr> <td>Postherpetic neuralgia</td><td>21</td><td>67% (14/21)</td><td>14% (4/21)<sup>f</sup></td><td>19% (3/21)<sup>f</sup></td></tr> <tr> <td>Anaesthesia dolorosa<sup>a</sup></td><td>18</td><td>39% (7/18)</td><td>44% (8/18)</td><td>17% (3/18)</td></tr> <tr> <td>Thalamic pain syndrome<sup>b</sup></td><td>14</td><td>43% (6/14)<sup>g</sup></td><td>29% (4/14)</td><td>29% (4/14)</td></tr> <tr> <td>Brachial plexus avulsion</td><td>11</td><td>36% (4/11)</td><td>36% (4/11)</td><td>27% (3/11)<sup>g</sup></td></tr> <tr> <td>Phantom and/or stump pain</td><td>10</td><td>50% (5/10)</td><td>20% (2/10)</td><td>30% (3/10)</td></tr> <tr> <td>Paraplegic pain<sup>c</sup></td><td>4</td><td>50% (2/4)</td><td>50% (2/4)</td><td>0</td></tr> <tr> <td>Other deafferentation pain<sup>d</sup></td><td>11</td><td>36% (4/11)</td><td>36% (4/11)</td><td>27% (3/11)<sup>g</sup></td></tr> <tr> <td>Total<sup>e</sup></td><td>89</td><td>47.2% (42/89)</td><td>31.5% (28/89)</td><td>21.3% (19/89)</td></tr> </table> <p><sup>a</sup>12 after ablative procedures or surgical nerve lesions who responded better than 6 patients with invasive cancer.</p> |                         |                         | Aetiology                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | No. of cases | Excellent | Improved | Failure | Postherpetic neuralgia | 21 | 67% (14/21) | 14% (4/21) <sup>f</sup> | 19% (3/21) <sup>f</sup> | Anaesthesia dolorosa <sup>a</sup> | 18 | 39% (7/18) | 44% (8/18) | 17% (3/18) | Thalamic pain syndrome <sup>b</sup> | 14 | 43% (6/14) <sup>g</sup> | 29% (4/14) | 29% (4/14) | Brachial plexus avulsion | 11 | 36% (4/11) | 36% (4/11) | 27% (3/11) <sup>g</sup> | Phantom and/or stump pain | 10 | 50% (5/10) | 20% (2/10) | 30% (3/10) | Paraplegic pain <sup>c</sup> | 4 | 50% (2/4) | 50% (2/4) | 0 | Other deafferentation pain <sup>d</sup> | 11 | 36% (4/11) | 36% (4/11) | 27% (3/11) <sup>g</sup> | Total <sup>e</sup> | 89 | 47.2% (42/89) | 31.5% (28/89) | 21.3% (19/89) | <p>Not reported</p> |
| Aetiology                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | No. of cases                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Excellent               | Improved                | Failure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| Postherpetic neuralgia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 21                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 67% (14/21)             | 14% (4/21) <sup>f</sup> | 19% (3/21) <sup>f</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| Anaesthesia dolorosa <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 18                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 39% (7/18)              | 44% (8/18)              | 17% (3/18)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| Thalamic pain syndrome <sup>b</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 43% (6/14) <sup>g</sup> | 29% (4/14)              | 29% (4/14)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| Brachial plexus avulsion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 36% (4/11)              | 36% (4/11)              | 27% (3/11) <sup>g</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| Phantom and/or stump pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 50% (5/10)              | 20% (2/10)              | 30% (3/10)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| Paraplegic pain <sup>c</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 50% (2/4)               | 50% (2/4)               | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| Other deafferentation pain <sup>d</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 36% (4/11)              | 36% (4/11)              | 27% (3/11) <sup>g</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
| Total <sup>e</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 89                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 47.2% (42/89)           | 31.5% (28/89)           | 21.3% (19/89)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                         |                         | <p><b>Follow-up issues:</b></p> <ul style="list-style-type: none"> <li>The percentages reported for pain relief do not resolve for many of the indications reported. It is not possible to determine whether the fraction or the numerator reported is inaccurate</li> </ul> <p><b>Study design issues:</b></p> <ul style="list-style-type: none"> <li>In 1983, use of an external receiver was replaced with a totally programmable implant by Medtronic.</li> <li>Patient recruitment not described.</li> <li>5-grade scale not described (ie. whether it was VAS).</li> </ul> <p><b>Study population issues:</b></p> <ul style="list-style-type: none"> <li>How 'intractable' was determined was not described (ie. how many previous treatments had failed).</li> </ul> |              |           |          |         |                        |    |             |                         |                         |                                   |    |            |            |            |                                     |    |                         |            |            |                          |    |            |            |                         |                           |    |            |            |            |                              |   |           |           |   |                                         |    |            |            |                         |                    |    |               |               |               |                     |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                     |          |
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| Study details                                                                                                                                                                                                                                                                                         | Key efficacy findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Key safety findings | Comments |
|                                                                                                                                                                                                                                                                                                       | <sup>b</sup> Success was inversely proportional to lesion size.<br><sup>c</sup> Patients had bilateral implantation of nucleus ventroposterolateralis thalami.<br><sup>d</sup> Included mixed pain such as phantom pain after amputation for brachial plexus avulsion.<br><sup>e</sup> Calculated by analyst.<br><sup>f</sup> as written in the study (unclear if the numerators or the percentages have been written incorrectly)<br><sup>g</sup> percentages calculated incorrectly in study |                     |          |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Study details                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Key efficacy findings                                                                                                                                                                                                                                                   | Key safety findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <p>Veloso F (1998)<sup>7</sup></p> <p><b>Case series</b></p> <p>Canada</p> <p>Recruitment period: 1979–1996/7</p> <p>Study population: patients with <b>benign intractable chronic pain syndromes</b></p> <p>n = <b>64</b></p> <p>Mean age: not reported</p> <p>Sex: 80% male</p> <p>Patient selection criteria: organic cause of pain, failure of conservative pain management methods, absence of psychiatric disorder, capacity to give consent, favourable response to double-blind morphine-naloxone test</p> <p>Technique: insertion of electrode into PAG (for nociceptive pain), ST, or IC (for deafferentation pain) with local anaesthetic, trial period of self-stimulation with external generator followed by internalisation of generator under general anaesthesia if satisfactory pain relief</p> <p>Mean follow-up: <b>6 months to 15 years</b></p> <p>Conflict of interest/source of funding: not reported</p> | <p>Number of patients analysed: <b>64</b></p> <p><b>Pain relief from trial stimulation</b></p> <p>79.7% (51/64) had satisfactory pain relief after the trial stimulation so had the procedure to internalize the electrodes. The others had the electrodes removed.</p> | <p><b>Presence of headache syndromes</b></p> <p>25% (16/64) of patients had headache symptoms after the procedure, ipsilateral only or worse on the ipsilateral side of the implantation.</p> <p>(6 of these had headaches before the procedure: 1 had no change in headache characteristics so was excluded from further analysis and 5 had significantly different headaches after.)</p> <p>In the majority of patients (53% [8/15]; study reported this as 54%), headache occurred between 1 and 2 months after the procedure. Onset in 7 patients ranged from less than 1 month to 18 months after the procedure. In the follow-up period, the duration of symptoms persisted for a mean 54 months. Headaches ceased in 13% (2/15) and subsided in intensity, duration and/or frequency in 33% (5/15).</p> <p>67% (10/15) of patients had recurrent headaches and 33% (5/15) had constant headaches.</p> <p>Most headache symptoms did not respond to pharmacological therapy but in 1 patient they responded to sumatriptan and in another they responded to lithium and then valproic acid.</p> <p>None of the patients who derived benefit from DBS but chose not to have internalisation of electrodes developed headaches.</p> | <p><b>Follow-up issues:</b></p> <ul style="list-style-type: none"> <li>All 64 patients were contacted by telephone (follow-up from 6 months to 15 years after procedure) to ask if they had any headaches. If any positive response, they attended a personal interview (6 unable to attend interview had a detailed telephone interview).</li> </ul> <p><b>Study design issues:</b></p> <ul style="list-style-type: none"> <li>Retrospective.</li> <li>Purpose of study to assess for headaches after DBS.</li> </ul> <p><b>Study population issues:</b></p> <ul style="list-style-type: none"> <li>Of those with headaches after the procedure, 14 were men and 2 were women; mean age 53 years old.</li> </ul> <p><b>Other issues:</b></p> <ul style="list-style-type: none"> <li>There were several cases of anomalies with the timing of headache development.</li> </ul> |

| Abbreviations used: CT, computerised tomography; DBS, deep brain stimulation; IC, internal capsule; MCS, motor cortex stimulation; MS, multiple sclerosis; PAG, periaqueductal grey matter; PVG, periventricular grey; SCS, spinal cord stimulation; ST, sensory thalamus; VAS, visual analogue scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                          |
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| Study details                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Key efficacy findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Key safety findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Comments                                                                                                                                                                                 |
| <p>Hemani C (2006)<sup>9</sup></p> <p><b>Case series</b></p> <p>Canada</p> <p>Recruitment period: 1992–2004</p> <p>Study population: patients with <b>refractory chronic neuropathic pain, characterised by burning, aching, dysesthesias and/or allodynia</b></p> <p>n = 21</p> <p>Mean age: 55 years</p> <p>Sex: 47.6% male</p> <p>Patient selection criteria: VAS of at least 6/10, refractory to medical therapies</p> <p>Exclusion criteria: significant psychological or psychosocial overlap and/or secondary gain as judged by a neurosurgical team</p> <p>Technique: insertion of electrode ventrocaudalis nucleus of the thalamus contralateral to the side of pain with a local anaesthetic (or medial lemniscus if entire hemibody was affected) and PAG/PVG if being treated for tactile allodynia (n = 8), trial period of macrostimulation to ensure no side effects followed by stimulation trial with external generator after 5 days followed by internalisation of generator under general anaesthesia if satisfactory pain relief (more than 50% in VAS)</p> <p>Median follow-up: <b>5 years (for 5 with prolonged insertional effect)</b></p> | <p>Number of patients analysed: <b>21</b></p> <p><b>Insertional effect</b></p> <p>43% (9/21) had an insertional effect (reduction of 60–100% of pain scores) after insertion of electrodes but before stimulation. It was not possible to tell if the stimulation was effective so these patients were not given stimulation unless they presented with a recurrence. Median time of recurrence of pain in these patients was 3 months (range: 10 days to 18 months).</p> <p><b>Pain relief from trial stimulation</b></p> <p>62% (13/21) patients with successful trial had implantation of the pulse generator.</p> <p>33% (7/21) did not have a significant pain relief so had their electrodes removed.</p> <p>One patient with a prolonged insertional effect was not stimulated.</p> <p>Of the 13 with successful stimulation, only 1 of the 5 with implants in both targets (ventrocaudalis nucleus and PVG/PAG) benefited and had both electrodes connected to a pulse generator. The other 12 had the generator connected to the electrodes in their ventrocaudalis nucleus.</p> <p><b>Long-term pain control</b></p> <p>Of the 21 patients initially implanted with DBS electrodes, 5 were still benefiting in the long-term at median 5 year follow-up (3 of these had originally had an insertional effect) and one had a prolonged insertional effect. 15 patients did not benefit from the procedure so discontinued treatment (7 after the trial and 8 in the first post-operative year).</p> | <p><b>Complications</b></p> <p>Occurred in 4 patients:</p> <ul style="list-style-type: none"> <li>1 patient had erosion in the region of the burr hole incision requiring removal of the system</li> <li>1 patient had seizure in the operating room during insertion of electrode</li> <li>1 patient had 2 consecutive infections requiring removal of parts of his DBS system</li> <li>1 patient with insertional effect for 4 months had an iatrogenic fracture of his electrodes when they were being reconnected to external cables for testing. This required a new surgical procedure to replace the fractured electrodes with new ones.</li> </ul> | <p><b>Study design issues:</b></p> <ul style="list-style-type: none"> <li>Retrospective review of medical records.</li> <li>Primary outcome was use of DBS at last follow-up.</li> </ul> |

|                                                                                                                                                                                                                                                                                                       |                               |                    |                  |                                     |                     |          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------|------------------|-------------------------------------|---------------------|----------|
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| Study details                                                                                                                                                                                                                                                                                         | Key efficacy findings         |                    |                  |                                     | Key safety findings | Comments |
| Conflict of interest/source of funding: not reported                                                                                                                                                                                                                                                  | Results by diagnosis          |                    |                  |                                     |                     |          |
|                                                                                                                                                                                                                                                                                                       | Diagnosis (No. of patients)   | Insertional effect | Successful trial | Using stimulation at last follow-up |                     |          |
|                                                                                                                                                                                                                                                                                                       | Post-stroke (8)               | 4                  | 4                | 0                                   |                     |          |
|                                                                                                                                                                                                                                                                                                       | Gunshot wound to the head (1) | 1                  | -                | -                                   |                     |          |
|                                                                                                                                                                                                                                                                                                       | Atypical facial pain (4)      | 1                  | 3                | 1                                   |                     |          |
|                                                                                                                                                                                                                                                                                                       | Phantom limb pain (1)         | 1                  | 1                | 1                                   |                     |          |
|                                                                                                                                                                                                                                                                                                       | Chiari/syrinx (1)             | 1                  | 1                | 1                                   |                     |          |
|                                                                                                                                                                                                                                                                                                       | Multiple sclerosis (2)        | 1                  | 1                | 1                                   |                     |          |
|                                                                                                                                                                                                                                                                                                       | Spinal cord injury (4)        | 0                  | 2                | 1                                   |                     |          |

## ***Efficacy***

A non-randomised comparative study of 43 patients with post-stroke pain reported a pain reduction greater than 60% in 25% (3/12) of patients treated with DBS and 48% (15/31) of patients treated with MCS (measured on a VAS [not described]; follow-up not reported)<sup>1</sup>.

A non-randomised comparative study of 19 patients with phantom limb pain reported a pain reduction greater than 80% in 60% (6/10) of patients treated with DBS and 20% (1/5) of patients treated with MCS in follow-ups ranging from 2 to 18 years (measured on a VAS [not described]). Four additional patients were treated with both DBS and MCS; 1 responded better to MCS and 2 responded better to DBS (response of fourth patient not reported)<sup>2</sup>.

A non-randomised comparative study of 10 patients with post-stroke pain reported a significant difference in pain reduction during the trial period in 3 of the 4 patients treated with DBS in one patients there was no significant difference (measured on McGill-Melzack pain scale, with high scores being worse; values ranged from 8.4 to 9 during 'off' periods and from 5 to 5.8 during 'on' periods,  $p < 0.02$ ). Of those treated with MCS, 50% (3/6) had no pain relief, 1 had pain relief for 31 months before dying of unrelated causes, 1 had pain relief for 2 to 3 weeks before dying of unrelated causes 7 months later and 1 had complete pain relief lasting 2 to 3 weeks at the time of the report<sup>3</sup>.

A meta-analysis of 6 case series, which included 424 patients treated with DBS for intractable pain, reported a significantly better success rate for patients with nociceptive pain compared with patients treated for deafferentation pain in follow-ups ranging from 1 month to 15 years (63% [129/204] vs 47% [103/220],  $p < 0.01$ , definition of success varied). The same study reported a significantly better success rate in those with peripheral deafferentation pain than those with central deafferentation pain in the same follow-up (51% [89/175] vs 31% [14/45],  $p < 0.03$ )<sup>4</sup>.

A case series of 112 patients with chronic intractable deafferentation pain reported that 89 patients had significant pain reduction after the test stimulation, so they received a permanent subcutaneous receiver. 'Excellent' results were reported in 47% (42/89) of patients, and 32% (28/89) of patients were considered to be 'improved' in follow-ups ranging from 6 months to 6 years ('excellent' was defined as pain-free [0 on a 0 to 5 scale, with 5 indicating worst pain], analgesic-free, and recovery to normal daily activities; 'improved' patients were those that scored 1 to 2 on the same pain scale). The treatments for the remaining patients were considered failures (21% [19/89], with scores of 3 or 4 on the pain scale)<sup>6</sup>.

A case series of 122 patients reported treatment success (defined as the patient being able to control their pain using the device with or without medication) in 77% (50/65) of patients with severe intractable pain of peripheral origin (follow-up not stated).

A case series of 21 patients with refractory chronic neuropathic pain reported an 'insertional effect' resulting in a 60–100% reduction in pain scores in 43% (9/21) of patients after insertion of the electrodes but before stimulation. This effect persisted without stimulation until recurrence occurred, at a median of 3 months, after which their electrodes were stimulated; 1 patient did not require stimulation because of a prolonged insertional effect<sup>9</sup>.

In the same study, 62% (13/21) of all patients with a successful trial received an implanted pulse generator. Six patients were still benefiting at median 5-year follow-up: 5 from long-term stimulation and 1 with a prolonged insertional effect (all others did not benefit from the procedure so had the system removed)<sup>9</sup>.

## **Safety**

### *Haemorrhage and death*

The case series of 141 patients with nociceptive or deafferentation pain reported intracranial haemorrhage in 4% (5/141) of patients; 1 patient died, 2 were left with significant deficits, and the deficit was completely resolved in 2 patients (time of occurrence not reported)<sup>5</sup>.

The case series of 122 patients reported 2 deaths: 1 happened 9 weeks after ventricular haemorrhage from a massive coronary occlusion and the other happened after an intracerebral haemorrhage because of massive cerebral oedema and haematoma in the basal ganglia. Another patient had an intracerebral haemorrhage and 2 more had ventricular haemorrhage, but these patients recovered<sup>8</sup>.

### *Infection*

The case series of 141 patients with nociceptive or deafferentation pain reported infection in 12% (17/141) of patients (23 cases) either within 30 days of the procedure (n = 12) or thereafter (n = 10) (occurrence of 1 not reported, mostly superficial infection apart from 1 with meningitis); 1 patient was successfully treated with antibiotics alone, 2 with antibiotics and debridement, and 11 with antibiotics and electrode removal (other 3 patients not described)<sup>5</sup>.

The case series of 122 patients reported ventriculitis in 1 patient, subgaleal infection in 4 patients and subdural empyema in 1 patient. The patient with ventriculitis and 3 of those with subgaleal infection were successfully treated with antibiotics but the remaining 2 patients required removal of the system hardware<sup>8</sup>.

The case series of 21 patients reported that 1 patient had 2 consecutive infections requiring removal of parts of his DBS system (time of occurrence not reported)<sup>9</sup>.

### *Device-related complications*

The case series of 141 patients reported major safety events related to the device: erosion of hardware in 7% (10/141) of patients, leakage of current into soft tissues usually from electrical insulation fractures in 9% (12/141) of patients, electrode migration resulting in failure in 10% (14/141), and other hardware failure in 4% (6/141). In the patients with device erosion, 5 patients had the system removed and 5 had successful re-implantation without antibiotics. Electrode migration occurred only with early versions of the electrodes. 'Other hardware failure' was not described but was resolved with the replacement of specific components<sup>5</sup>.

The same study reported foreign body reaction in 5% (7/141) of patients, requiring removal of the DBS system in 4 patients<sup>5</sup>.

The case series of 122 patients reported erosion of the scalp overlying the connector in 2 patients at 1 and 1.5 years, and electrode migration resulting in no pain relief in 2 patients (scalp erosion required plastic repair of scalp but sequelae not described for electrode migration)<sup>8</sup>.

The case series of 21 patients reported that 1 patient had erosion in the region of the burr hole incision requiring removal of the system and another had iatrogenic electrode fracture when they were being reconnected to external cables for testing, requiring a procedure to replace the fractured electrodes with new ones (time of occurrence not reported)<sup>9</sup>.

### *Other*

The case series of 141 patients with nociceptive or deafferentation pain reported psychosis in 2% (3/141) of patients; 2 of these had a history of drug abuse<sup>5</sup>.

The same study reported minor complications including headache (mostly transient) in 51% (72/141) of patients, diplopia caused by air/contrast ventriculography and PAG/PVG stimulation in 14% (20/141), nausea in 11% (15/141), vertical gaze palsies in 10% (14/141), blurred vision in 9% (13/141), hemi-or monoparesis in 9% (12/141), confusion in 8% (11/141), lethargy in 6% (9/141), dysphasia in 6% (8/141), and local pain in 5% (7/141) of patients. Events that occurred each in less than 5% of patients included horizontal nystagmus, persistent oscillopsia, seizures, urinary incontinence, cranial nerve palsies, ptosis, urinary retention, bronchospasm, hypesthesia, hallucinations, photophobia, memory loss, hypotension, facial pain, hypertension, shortness of breath, dysphoria, thrombophlebitis, and stimulation-induced sleep.

The case series of 122 patients reported permanent eye movement dysfunction in 3 patients that was thought to be caused by a particular placement of the tip of the electrode. This was considered to be avoided in future treated patients by moving the tip caudally<sup>8</sup>.

The study of 64 patients treated with DBS for nociceptive or deafferentation pain reported that 25% (16/64) of patients had headache symptoms which occurred 1 to 2 months after the procedure in the majority of patients. Six of these patients reported headaches before implantation but the headaches were unchanged in 1 and significantly different in 5 (not clear if headaches were worse or better)<sup>7</sup>.

The non-randomised study of 10 patients with post-stroke pain reported that 1 of the 4 patients treated with DBS developed a CSF leak when the electrode was being inserted into the PVG, so the electrode was not implanted. This patient had a haematoma over the pulse generator site (no more details provided)<sup>3</sup>.

The case series of 21 patients reported that 1 patient had a seizure in the operating room during insertion of an electrode (no sequelae described)<sup>9</sup>.

### ***Validity and generalisability of the studies***

- The evidence on this procedure includes publications from as early as the late 1970s (see appendix A). The studies included in table 2 span from the late 1980s to 2002 but there are some more recent, smaller publications in appendix A.
- Evidence includes several different aetiologies of chronic pain and the efficacy of the procedure appears to vary for the type of pain (for example, nociceptive and deafferentation) and by aetiology.
- There are a limited number of non-randomised comparative studies which are relatively small in size and sometimes lacking in detail<sup>1,2,3</sup>.
- Several studies did not report safety data and this is limited to only 3 studies in the table<sup>3,7,5</sup>. Two of these studies report a large number of safety events but they were published over 20 years ago so some events may relate to earlier versions of the device and/or techniques<sup>5,8</sup>.

### ***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 (2003). Available from [www.nice.org.uk/guidance/IPG19](http://www.nice.org.uk/guidance/IPG19)

- 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](http://www.nice.org.uk/guidance/IPG188)
- Non-rigid stabilisation techniques for the treatment of low back pain. NICE interventional procedures guidance 183 (2006). Available from [www.nice.org.uk/guidance/IPG183](http://www.nice.org.uk/guidance/IPG183)
- Prosthetic intervertebral disc replacement in the lumbar spine. NICE interventional procedures guidance 306 (2009). Available from [www.nice.org.uk/guidance/IPG306](http://www.nice.org.uk/guidance/IPG306)
- Percutaneous intradiscal electrothermal therapy for low back pain. NICE interventional procedures guidance 319 (2009). Available from [www.nice.org.uk/guidance/IPG319](http://www.nice.org.uk/guidance/IPG319)
- Lateral (including extreme, extra and direct lateral) interbody fusion in the lumbar spine. NICE interventional procedures guidance 321 (2009). Available from [www.nice.org.uk/guidance/IPG321](http://www.nice.org.uk/guidance/IPG321)
- Percutaneous disc decompression using coblation for lower back pain. NICE interventional procedures guidance 173 (2006). Available from [www.nice.org.uk/guidance/IPG173](http://www.nice.org.uk/guidance/IPG173)
- Percutaneous intradiscal radio frequency thermo coagulation for lower back pain. NICE interventional procedures guidance 83 (2004). Available from [www.nice.org.uk/guidance/IPG83](http://www.nice.org.uk/guidance/IPG83)

### Technology appraisals

- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal 159 (2008). Available from [www.nice.org.uk/guidance/TA159](http://www.nice.org.uk/guidance/TA159)

### Clinical guidelines

- Early management of persistent non-specific low back pain. NICE clinical guideline 88 (2009). Available from [www.nice.org.uk/guidance/CG88](http://www.nice.org.uk/guidance/CG88)

## 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 Jon Raphael, Professor Turo Nurmikko, British Pain Society; Mr Sam Eljamel, Mr Surajit Basu, Society for British Neurological Surgeons.

- One Adviser has not performed this procedure but takes part in selection for this procedure; two Advisers have performed the procedure at least once.

- Comparators include medical management, alternative stimulation (spinal cord stimulation or motor cortex stimulation) and sometimes destructive neurosurgery.
- There is uncertainty about the efficacy of the procedure. There are no randomised controlled trials. Early literature was variable in the targets selection but consensus has emerged over time (one Adviser commented that simultaneous stimulation of the thalamus and periventricular grey provides the best result).
- One Adviser commented that the use of DBS for pain has decreased significantly with the advent of chronic pain management and extracranial procedures (less than 10% of specialists perform this procedure).
- Patient selection for this procedure is important.
- Anecdotal adverse events included the suspected development of a new neuropathic pain condition after migration of the lead, mood change from aberrant stimulation, stimulation-induced reversible side effects such as dysarthria, temporary or permanent neurological sequelae, seizures, infection, skin erosion and hardware complications such as lead misplacement, lead migration, or lead fractures.
- Theoretical adverse events include cerebral haemorrhage, cerebral infarction if inappropriate imaging used, intracranial infection, migration of the lead with subsequent neurological sequelae, and cognitive changes.
- Key efficacy outcomes include reduction in frequency and severity of pain, improvement in physical and mental function, improvement in quality of life, and reduction in medication requirements.

## **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 (8 were related to chronic pain syndromes and 3 were related to trigeminal autonomic cephalalgias).

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:

- Strongly positive commentaries were received from patients who had been treated by DBS; some described how even partial relief of their pain had resulted in significantly improved quality of life.

## **Issues for consideration by IPAC**

- An RCT that started in May 2010 will compare DBS with sham for thalamic pain syndrome (NCT01072656; funded by The Cleveland Clinic in

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collaboration with the National Institute for Health; estimated enrollment, 34 patients; estimated completion mid-2014).

- Patients with chronic pain syndromes are likely to be considered to have a disability by the Disability Discrimination Act since it is likely to have a significant impact on their daily activities of living.

## References

1. Katayama Y, Yamamoto T, Kobayashi K et al. (2001) Motor cortex stimulation for post-stroke pain: comparison of spinal cord and thalamic stimulation. *Stereotactic and Functional Neurosurgery* 77: 183–6.
2. Katayama Y, Yamamoto T, Kobayashi K et al. (2001) Motor cortex stimulation for phantom limb pain: comprehensive therapy with spinal cord and thalamic stimulation. *Stereotactic and Functional Neurosurgery* 77: 159–162.
3. Nandi D, Smith H, Owen S et al. (2002) Peri-ventricular grey stimulation versus motor cortex stimulation for post stroke neuropathic pain. *Journal of Clinical Neuroscience* 9: 557–61.
4. Bittar RG, Kar-Purkayastha I, Owen SL et al. (2005) Deep brain stimulation for pain relief: a meta-analysis. *Journal of Clinical Neuroscience* 12: 515–9.
5. Levy RM, Lamb S, Adams JE (1987) Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. *Neurosurgery* 21: 885–93.
6. Siegfried J (1987) Sensory thalamic neurostimulation for chronic pain. *Pacing and Clinical Electrophysiology* 10: 209–12.
7. Veloso F, Kumar K, Toth C (1998) Headache secondary to deep brain implantation. *Headache* 38: 507–15.
8. Hosobuchi Y (1986) Subcortical electrical stimulation for control of intractable pain in humans. *Journal of Neurosurgery* 64:543–53.
9. Hamani C, Schwalb JM, Rezai AR et al. (2006) Deep brain stimulation for chronic neuropathic pain: long-term outcome and the incidence of insertional effect. *Pain* 125: 188–96.

## **Appendix A: Additional papers on deep brain stimulation for chronic pain syndromes (excluding headache)**

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 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Baskin DS, Mehler WR, Hosobuchi Y et al. (1986) Autopsy analysis of the safety, efficacy and cartography of electrical stimulation of the central gray in humans. Brain Research 371: 231–6.                 | Case series<br>n = 7 (6 with cancer and 1 with diabetic neuropathy) had PVG or PAG implantation                         | Each had complete pain relief. This declined over a period of 6 to 10 weeks in 3 patients. All patients later died because of causes related to their primary disease.                                                                                                                                                                       | Larger studies included in table 2.  |
| Bittar RG, Otero S, Carter H et al. (2005) Deep brain stimulation for phantom limb pain. Journal of Clinical Neuroscience 12: 399–404.                                                                       | Case series<br>n = 3 with phantom limb pain<br>Mean follow-up = 13.3 months                                             | Pain intensity decreased 62% at last follow-up. In all patients, the burning component was completely alleviated. Quality of life was significantly improved.                                                                                                                                                                                | Larger studies in table 2.           |
| Cordella R, Franzini A, La ML et al. (2009) Hypothalamic stimulation for trigeminal neuralgia in multiple sclerosis patients: efficacy on the paroxysmal ophthalmic pain. Multiple Sclerosis 15: 1322–8.     | Case series<br>n = 5 with multiple sclerosis<br>Follow-up = 1 month to 4 years                                          | Paroxysmal pain arising from first trigeminal branch was controlled but recurrence of pain in 2nd and 3rd trigeminal branch required thermorhizotomies to control the pain in 2 patients after 2 years of follow-up.                                                                                                                         | Larger studies in table 2.           |
| Duncan GH, Kupers RC, Marchand S et al. (1998) Stimulation of human thalamus for pain relief: possible modulatory circuits revealed by positron emission tomography. Journal of Neurophysiology 80: 3326–30. | Case series<br>n = 5 with chronic neuropathic pain                                                                      | All had satisfactory pain relief for more than 3 years. All patients had paresthesia during stimulation.                                                                                                                                                                                                                                     | Larger studies in table 2.           |
| Franzini A, Leone M, Messina G et al. (2008) Neuromodulation in treatment of refractory headaches. Neurological Sciences 29: Suppl. 8.                                                                       | Case series<br>n = 8 (5 with MS and trigeminal neuralgia and 3 with atypical facial pain)<br>Mean follow-up = 24 months | 71% of postoperative days were pain-free and intensity and duration of pain was significantly reduced. Mean time to stable benefit was 48 days. Drugs were reduced to less than 20% of preoperative level. No improvement in facial pain; 2 of 5 with MS-related neuralgia were pain-free at follow-up and other 3 had improved pain relief. | Larger studies in table 2.           |
| Green AL, Wang S, Owen SL et al. (2004) Controlling the heart via the brain: a potential new therapy for orthostatic hypotension.                                                                            | Case series<br>n = 11 with chronic neuropathic pain                                                                     | Purpose was to look at the effect on blood pressure. Systolic blood pressure decreased on standing from 28.2% to 11.1% in 1 patient with                                                                                                                                                                                                     | Larger studies in table 2.           |

|                                                                                                                                                                           |                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                               |                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Neurosurgery 58: 1176–83.                                                                                                                                                 |                                                                                                                      | orthostatic hypotension ( $p < 0.001$ ). In those with mild orthostatic intolerance, there was a significant drop in systolic blood pressure (15.4% drop, $p < 0.001$ ).                                                                                                                                                                                                                                      |                                     |
| Green AL, Shad A, Watson R et al. (2004) N-of-1 Trials for Assessing the Efficacy of Deep Brain Stimulation in Neuropathic Pain. Neuromodulation 7: 76–81.                | Case series<br>n = 7 with intractable neuropathic pain<br>Follow-up = 6 months                                       | VAS scores significantly reduced in 6 of the 7 patients. McGill Pain Scores showed pain reduction in 4 of the 7.                                                                                                                                                                                                                                                                                              | Larger studies in table 2.          |
| Green AL, Wang S, Owen SL et al. (2006) Stimulating the human midbrain to reveal the link between pain and blood pressure. Pain 124: 349–59.                              | Case series<br>n = 16 with chronic neuropathic pain<br>Follow-up = 1 year                                            | Purpose was to test association between blood pressure and pain relief.<br><br>Mean pain score decreased from 34 at baseline to 12.2 at 1 year ( $p = 0.003$ ) (McGill pain questionnaire 0 – 50, with 50 being worse pain imaginable).                                                                                                                                                                       | Larger studies in table 2.          |
| Green AL, Wang S, Bittar RG et al. (2007) Deep brain stimulation: a new treatment for hypertension? Journal of Clinical Neuroscience 14: 592–5.                           | Case report<br>n = 1 with intractable neuropathic pain affecting soft palate, oral cavity and lateral side of tongue | Patient had both pain relief and blood pressure reduction with stimulation of the ventro-posteromedial nucleus of the thalamus.                                                                                                                                                                                                                                                                               | Larger studies included in table 2. |
| Kringelbach ML, Jenkinson N, Green AL et al. (2007) Deep brain stimulation for chronic pain investigated with magnetoencephalography. Neuroreport 18: 223–8.              | Case report<br>n = 1 with phantom limb pain                                                                          | Patient had 'excellent' pain relief after the procedure. The electrode later fractured after the patient fell, which resulted in the pain returning. Surgical revision was required and pain relief returned.                                                                                                                                                                                                 | Larger studies in table 2.          |
| Kumar K, Wyant GM, and Nath R (1990) Deep brain stimulation for control of intractable pain in humans, present and future: a ten-year follow-up. Neurosurgery 26: 774–81. | Case series<br>n = 48<br>Follow-up = 6 months to 10 years                                                            | Long-term pain control in 63% (30/48). There was an initial 2-year 'fall-off' of pain control but stable results after this regardless of implantation site. Those with failed-back syndrome secondary to multiple disc operations did well; pain secondary to progressive neurological disorders had short-term pain relief; those with thalamic pain, cauda equine injury, or phantom limb pain did poorly. | Larger studies in table 2.          |

|                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                      |                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Kumar K, Toth C, Nath R (1997) Deep brain stimulation for intractable pain: A 15-year experience. <i>Neurosurgery</i> 40: 736–47.                                                             | Case series<br>n = 68<br>Mean follow-up = 78 months                                                                                                                                                                                                                                                                                       | 77% (53/68) had internalisation of their devices.<br>79% (42/53) continued to have adequate pain relief (measured using McGill Pain Questionnaire).<br>Patient with failed back syndrome, trigeminal neuropathy and peripheral neuropathy did well but thalamic pain, spinal cord injury and postherpetic neuralgia did not do well. | Larger studies in table 2 (and study included in Bittar <sup>4</sup> ). |
| Kupers RC, Gybels JM, and Gjedde A (2000) Positron emission tomography study of a chronic pain patient successfully treated with somatosensory thalamic stimulation. <i>Pain</i> 87: 295–302. | Case report<br>n = 1 with pain after adenocarcinoma was resected from the right cheek                                                                                                                                                                                                                                                     | Patient was pain-free during normal use of the stimulator.                                                                                                                                                                                                                                                                           | Larger studies in table 2.                                              |
| Marchand S, Kupers RC, Bushnell MC et al. (2003) Analgesic and placebo effects of thalamic stimulation. <i>Pain</i> 105: 481–8.                                                               | Case series<br>n = 6 (with trigeminal pain [3], trigeminal neuralgia of unknown origin [2], surgical excision of ameloblastoma of left mandible [1], post-surgical pain affecting left eye orbit [1], chronic pain in right leg from central post-traumatic lesion [1], cervico-brachialgia after accidental nervous plexus avulsion [1]) | Percent pain reduction measured at home on VAS was lower than before the pre-experimental ratings.<br>Perceived intensity and unpleasantness were rated significantly lower during days with DBS compared with days without simulation.                                                                                              | Larger studies in table 2.                                              |
| Munding F and Salomao JF (1980) Deep brain stimulation in mesencephalic lemniscus medialis for chronic pain. <i>Acta Neurochirurgica - Supplementum</i> 30: 245–58.                           | Case series<br>n = 32<br>Follow-up = 47 months                                                                                                                                                                                                                                                                                            | Stimulation in lemniscus medialis showed a 50% reduction in pain in 53% of cases.                                                                                                                                                                                                                                                    | Larger studies included in table 2.                                     |
| Nandi D, Aziz T, Carter H et al. (2003) Thalamic field potentials in chronic central pain treated by periventricular gray stimulation – a series of eight cases. <i>Pain</i> 101: 97–107.     | Case series<br>n = 8 with chronic central pain<br>Follow-up = 9 months                                                                                                                                                                                                                                                                    | 6 patients had implanted PVG procedure because of satisfactory pain relief .<br>4 had ventroposterolateral thalamic nucleus stimulation (these had MS, pontine tractotomy, stroke, and Chiari                                                                                                                                        | Larger studies included in table 2.                                     |

|                                                                                                                                                                                                                                                                                                 |                                                                                  |                                                                                                                                                                                                                                                                                            |                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
|                                                                                                                                                                                                                                                                                                 |                                                                                  | malformation) but 2 had significant persistent paresthesia so did not continue.                                                                                                                                                                                                            |                                     |
| Nandi D, Aziz TZ (2004) Deep brain stimulation in the management of neuropathic pain and multiple sclerosis tremor. <i>Journal of Clinical Neurophysiology</i> 21: 31–9.                                                                                                                        | Case series<br>n = 19 (14 with post-stroke pain)<br>Follow-up = 16 months        | 13 had satisfactory pain relief which was maintained over follow-up in all but 2 patients.                                                                                                                                                                                                 | Larger studies included in table 2. |
| Owen SL, Green AL, Stein JF et al. (2006) Deep brain stimulation for the alleviation of post-stroke neuropathic pain. <i>Pain</i> 120: 202–6.                                                                                                                                                   | Case series<br>n = 15 with post-stroke neuropathic pain<br>Follow-up = 27 months | 48.8% improvement in mean scores on VAS but this varied greatly between patients ( $p < 0.001$ ).<br><br>3 had no significant pain relief and did not need to have implantation of generator.<br><br>1 case of fractured extension lead with head injury which required surgical revision. | Larger studies in table 2.          |
| Owen SL, Heath J, Kringelbach M et al. (2008) Pre-operative DTI and probabilistic tractography in four patients with deep brain stimulation for chronic pain. <i>Journal of Clinical Neuroscience</i> 15: 801–5.                                                                                | Case series<br>n = 4 with chronic neuropathic pain (2 after stroke)              | 1 patient required explantation because of no benefit after 1 week.<br><br>The other 3 had good results but in 1 patient, the wire broke so the stimulator was then explanted.                                                                                                             | Larger studies in table 2.          |
| Pickering AE, Thornton SR, Love-Jones SJ et al. (2009) Analgesia in conjunction with normalisation of thermal sensation following deep brain stimulation for central post-stroke pain. <i>Pain</i> 147: 299–304.                                                                                | Case report<br>n = 1 with post-stroke pain                                       | Initial improvement in pain but pain control gradually deteriorated 4 months later. In the following year, the patient reported worsening of pain when the generator was switched on.                                                                                                      | Larger studies in table 2.          |
| Previnaire JG, Nguyen JP, Perrouin-Verbe B et al. (2009) Chronic neuropathic pain in spinal cord injury: efficiency of deep brain and motor cortex stimulation therapies for neuropathic pain in spinal cord injury patients. <i>Annals of Physical and Rehabilitation Medicine</i> 52: 188–93. | Systematic review                                                                | Studies included in this review are already included in this overview.                                                                                                                                                                                                                     | No new information.                 |
| Richardson RR, Meyer PR, Cerullo LJ (1980)                                                                                                                                                                                                                                                      | Case series                                                                      | Better pain relief in the second group (traumatic                                                                                                                                                                                                                                          | Larger studies in table             |

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Neurostimulation in the modulation of intractable paraplegic and traumatic neuroma pains. Pain 8: 75–84.                                                                                 | n = 19 (10 with intractable paraplegic pain and 9 with traumatic neuroma pain)                           | neuroma pain).<br>4 patients in the first group did not have permanent neurostimulator. Of the remaining 6, only 1 had significant pain relief at 1 year. In the second group, only 3 did not have significant pain relief at 1 year.                                                        | 2.                                                                      |
| Romanelli P and Heit G (2004) Patient-controlled deep brain stimulation can overcome analgesic tolerance. Stereotactic and Functional Neurosurgery 82: 77–9.                             | Case report<br>n = 1 with post-stroke pain                                                               | Patient had excellent pain control for 13 months but then required changes in the stimulation over the following 20 months as pain attacks progressed in frequency but with only some relief. A patient-controlled device was then placed resulting in excellent pain control.               | Larger studies in table 2.                                              |
| Shulman R, Turnbull IM, Diawold P (1982) Psychiatric aspects of thalamic stimulation for neuropathic pain. Pain 13: 127–35.                                                              | Case series<br>n = 24<br>mean follow-up = more than 2 years                                              | Unsuccessful in 6 patients.<br>18 had complete or partial relief.                                                                                                                                                                                                                            | Larger studies in table 2.                                              |
| Spooner J, Yu H, Kao C et al. (2007) Neuromodulation of the cingulum for neuropathic pain after spinal cord injury. Case report. Journal of neurosurgery 107: 169–72.                    | Case report<br>n = 1 after spinal cord injury                                                            | Stimulation from an electrode in the cingulum was more successful at pain control than one inserted into the periventricular grey matter.                                                                                                                                                    | Larger studies in table 2.                                              |
| Turnbull IM, Shulman R, Woodhurst WB (1980) Thalamic stimulation for neuropathic pain. Journal of Neurosurgery 52: 486–93.                                                               | Case series<br>n = 18                                                                                    | 14 patients had satisfactory pain relief so had internalisation of system. 12 of these continued to have complete or partial pain relief with regular stimulation.<br>2 did not have treatment because of inability to locate the target (2) or failure to fix the electrode adequately (1). | Larger studies in table 2 (and study included in Bittar <sup>4</sup> ). |
| Yamamoto T, Katayama Y, Obuchi T et al. (2006) Thalamic sensory relay nucleus stimulation for the treatment of peripheral deafferentation pain. Stereotactic and Functional Neurosurgery | Case series<br>n = 18 (11 with phantom limb pain and 7 with pain from root or nerve injury)<br>Follow-up | Patients in both groups had pain reduction on VAS (66.4% reduction in pain on VAS with 78% [14/18] who had greater than 60% reduction).                                                                                                                                                      | Larger studies in table 2.                                              |

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| 84: 180–3.                                                                                                                                                                  |                                                                                 |                                                                                                                                                                                                                  |                                         |
| Young RF, Brechner T (1986) Electrical stimulation of the brain for relief of intractable pain due to cancer. Cancer 57: 1266–72.                                           | Case series<br>n = 17 with cancer-related pain<br>Follow-up from 1 to 21 months | 13 patients had total pain relief and 2 had partial pain relief.<br>6 patients were alive at follow-up; 14 required narcotics for pain relief later, usually in the terminal few weeks of their life.            | Larger studies in table 2.              |
| Young RF, Kroening R, Fulton W et al. (1985) Electrical stimulation of the brain in treatment of chronic pain: Experience over 5 years. Journal of Neurosurgery 62: 389–96. | Case series<br>n = 48 with chronic pain<br>Mean follow-up = 20 months           | 72% of patients had complete or partial relief. 59% were able to stop using narcotics. 25% returned to normal physical activity and 33% had marked improvement in functional capacity. Only minor complications. | Study included in Bittar <sup>4</sup> . |

## Appendix B: Related NICE guidance for deep brain stimulation for chronic pain syndromes (excluding headache)

| Guidance                  | Recommendations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Interventional procedures | <p><b>Deep brain stimulation for Parkinson's disease. NICE interventional procedures guidance 19 (2003)</b></p> <p>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.</p> <p>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 (<a href="http://www.pdsurg.bham.ac.uk">www.pdsurg.bham.ac.uk</a>).</p> <p>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.</p> <p><b>Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). NICE interventional procedures guidance 188 (2006)</b></p> <p>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.</p> <p>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.</p> <p><b>Non-rigid stabilisation techniques for the treatment of low back pain. NICE interventional procedures guidance 183 (2006).</b></p> <p>1.1 Limited evidence suggests that non-rigid stabilisation procedures for the treatment of low back pain provide clinical benefit for a proportion of patients with intractable back pain. Current evidence on the safety of these procedures is unclear and involves a variety of different devices and outcome measures. Therefore, these procedures should only be used with special arrangements for consent and for audit or research.</p> <p>1.2 Clinicians wishing to undertake non-rigid stabilisation techniques for the treatment of low back pain should take the following actions.</p> <ul style="list-style-type: none"> <li>• Inform the clinical governance leads in their Trusts.</li> </ul> |

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|  | <ul style="list-style-type: none"> <li>• Ensure that patients understand the uncertainty about the benefits of these procedures and the alternative treatment options, and provide them with clear written information. In addition, use of the Institute's 'Understanding NICE guidance' is recommended (available from <a href="http://www.nice.org.uk/IPG183publicinfo">www.nice.org.uk/IPG183publicinfo</a>).</li> <li>• Audit and review clinical outcomes of all patients undergoing non-rigid stabilisation procedures for the treatment of low back pain.</li> </ul> <p>1.3 Publication of further research will be useful provided that the outcome measures and comparators are well defined. The Institute may review the procedure upon publication of further evidence.</p> <p><b>Prosthetic intervertebral disc replacement in the lumbar spine. NICE interventional procedures guidance 306 (2009).</b></p> <p>1.1 Current evidence on the safety and efficacy of prosthetic intervertebral disc replacement in the lumbar spine is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit.</p> <p>1.2 A multidisciplinary team with specialist expertise in the treatment of degenerative spine disease should be involved in patient selection for prosthetic intervertebral disc replacement in the lumbar spine. The procedure should only be carried out in patients for whom conservative treatment options have failed or are contraindicated.</p> <p>1.3 The current evidence includes studies with a maximum follow-up of 13 years, but the majority of evidence is from studies with shorter durations of follow-up. NICE encourages clinicians to continue to collect and publish data on longer-term outcomes, which should include information about patient selection and the need for further surgery.</p> <p><b>Percutaneous intradiscal electrothermal therapy for low back pain. NICE interventional procedures guidance 319 (2009).</b></p> <p>1.1 Current evidence on the safety and efficacy of percutaneous intradiscal electrothermal therapy for low back pain is inconsistent. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.</p> <p>1.2 Clinicians wishing to undertake percutaneous intradiscal electrothermal therapy for low back pain should take the following actions.</p> <ul style="list-style-type: none"> <li>• Inform the clinical governance leads in their Trusts.</li> <li>• Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from <a href="http://www.nice.org.uk/IPG319publicinfo">www.nice.org.uk/IPG319publicinfo</a>).</li> <li>• Audit and review clinical outcomes of all patients having percutaneous intradiscal electrothermal therapy for low back pain (see section 3.1).</li> </ul> |
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|  | <p>1.3 NICE encourages further research into percutaneous intradiscal electrothermal therapy for low back pain. Research should describe patient selection, use validated measures of long-term pain relief and quality of life, address the role of the procedure in avoiding major surgery, and measure long-term safety outcomes.</p> <p><b>Lateral (including extreme, extra and direct lateral) interbody fusion in the lumbar spine. NICE interventional procedures guidance 321 (2009).</b></p> <p>1.1 Current evidence on the safety and efficacy of lateral (including extreme, extra and direct lateral) interbody fusion in the lumbar spine is inadequate in quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.</p> <p>1.2 Clinicians wishing to undertake lateral interbody fusion in the lumbar spine should take the following actions.</p> <ul style="list-style-type: none"> <li>• Inform the clinical governance leads in their Trusts.</li> <li>• Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from <a href="http://www.nice.org.uk/IPG321publicinfo">www.nice.org.uk/IPG321publicinfo</a>).</li> <li>• Audit and review clinical outcomes of all patients having lateral interbody fusion in the lumbar spine (see section 3.1).</li> </ul> <p>1.3 This procedure should only be carried out by surgeons with specific training in the technique, who should perform their initial procedures with an experienced mentor.</p> <p>1.4 NICE encourages further research into lateral interbody fusion in the lumbar spine. Research outcomes should include fusion rates, pain and functional scores, quality of life measures and the frequency of both early and late complications. NICE may review the procedure on publication of further evidence.</p> <p><b>Percutaneous disc decompression using coblation for lower back pain. NICE interventional procedures guidance 173 (2006).</b></p> <p>1.1 Current evidence suggests that there are no major safety concerns associated with the use of percutaneous disc decompression using coblation for lower back pain. There is some evidence of short-term efficacy; however, this is not sufficient to support the use of this procedure without special arrangements for consent and for audit or research.</p> <p>1.2 Clinicians wishing to undertake percutaneous disc decompression using coblation for lower back pain should take the following actions.</p> <ul style="list-style-type: none"> <li>• Inform the clinical governance leads in their Trusts.</li> <li>• Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. Use of the Institute's <i>Information for the public</i> is recommended (available from</li> </ul> |
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|  | <p><a href="http://www.nice.org.uk/IPG173publicinfo">www.nice.org.uk/IPG173publicinfo</a>).</p> <ul style="list-style-type: none"> <li>• Audit and review clinical outcomes of all patients having percutaneous disc decompression using coblation for lower back pain.</li> </ul> <p>1.3 Further research will be useful in reducing the current uncertainty, and clinicians are encouraged to collect long-term follow-up data. The Institute may review the procedure upon publication of further evidence.</p> <p><b>Percutaneous intradiscal radiofrequency thermocoagulation for lower back pain. NICE interventional procedures guidance 83 (2004).</b></p> <p>1.1 Current evidence on the safety and efficacy of percutaneous intradiscal radiofrequency thermocoagulation for lower back pain does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research.</p> <p>1.2 Clinicians wishing to undertake percutaneous intradiscal radiofrequency thermocoagulation for lower back pain should take the following actions.</p> <ul style="list-style-type: none"> <li>• Inform the clinical governance leads in their Trusts.</li> <li>• Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. Use of the Institute's <i>Information for the Public</i> is recommended.</li> <li>• Audit and review clinical outcomes of all patients having percutaneous intradiscal radiofrequency thermocoagulation for lower back pain.</li> </ul> <p>1.3 Further research will be useful in reducing the current uncertainty and clinicians are encouraged to collect longer-term follow-up data. The Institute may review the procedure upon publication of further evidence.</p> |
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| Technology appraisals | <p><b>Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal 159 (2008).</b></p> <p>1.1 Spinal cord stimulation is recommended as a treatment option for adults with chronic pain of neuropathic origin who:</p> <ul style="list-style-type: none"> <li>• continue to experience chronic pain (measuring at least 50 mm on a 0–100 mm visual analogue scale) for at least 6 months despite appropriate conventional medical management, and</li> <li>• who have had a successful trial of stimulation as part of the assessment specified in recommendation 1.3.</li> </ul> <p>1.2 Spinal cord stimulation is not recommended as a treatment option for adults with chronic pain of ischaemic origin except in the context of research as part of a clinical trial. Such research should be designed to generate robust evidence about the benefits of spinal cord stimulation (including pain relief, functional outcomes and quality of life) compared with standard care.</p> <p>1.3 Spinal cord stimulation should be provided only after an assessment by a multidisciplinary team experienced in chronic pain assessment and management of people with spinal cord stimulation devices, including experience in the provision of ongoing monitoring and support of the person assessed.</p> <p>1.4 When assessing the severity of pain and the trial of stimulation, the multidisciplinary team should be aware of the need to ensure equality of access to treatment with spinal cord stimulation. Tests to assess pain and response to spinal cord stimulation should take into account a person's disabilities (such as physical or sensory disabilities), or linguistic or other communication difficulties, and may need to be adapted.</p> <p>1.5 If different spinal cord stimulation systems are considered to be equally suitable for a person, the least costly should be used. Assessment of cost should take into account acquisition costs, the anticipated longevity of the system, the stimulation requirements of the person with chronic pain and the support package offered.</p> <p>1.6 People who are currently using spinal cord stimulation for the treatment of chronic pain of ischaemic origin should have the option to continue treatment until they and their clinicians consider it appropriate to stop.</p> |
| Clinical guidelines   | <p><b>Early management of persistent non-specific low back pain. NICE clinical guideline 88 (2009).</b></p> <p><b>1 Guidance</b></p> <p><b>1.1 Assessment and imaging</b></p> <p>1.1.1 Keep diagnosis under review.</p> <p>1.1.2 Do not offer X-ray of the lumbar spine for the management of non-specific low back pain.</p> <p>1.1.3 Consider MRI (magnetic resonance imaging) when a diagnosis of spinal malignancy, infection, fracture, cauda equina syndrome or ankylosing spondylitis or another inflammatory disorder is suspected.</p> <p>1.1.4 Only offer an MRI scan for non-specific low back pain within the context of a referral for an opinion on spinal fusion</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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|  | <p>(see section 1.9).</p> <p><b>1.2 Information, education and patient preferences</b></p> <p>1.2.1 Provide people with advice and information to promote self-management of their low back pain.</p> <p>1.2.2 Offer educational advice that:</p> <ul style="list-style-type: none"> <li>• includes information on the nature of non-specific low back pain</li> <li>• encourages the person to be physically active and continue with normal activities as far as possible.</li> </ul> <p>1.2.3 Include an educational component consistent with this guideline as part of other interventions, but do not offer stand-alone formal education programmes.</p> <p>1.2.4 Take into account the person's expectations and preferences when considering recommended treatments, but do not use their expectations and preferences to predict their response to treatments.</p> <p>1.2.5 Offer one of the following treatment options, taking into account patient preference: an exercise programme (see section 1.3.3), a course of manual therapy (see section 1.4.1) or a course of acupuncture (see section 1.6.1). Consider offering another of these options if the chosen treatment does not result in satisfactory improvement.</p> <p><b>1.3 Physical activity and exercise</b></p> <p>1.3.1 Advise people with low back pain that staying physically active is likely to be beneficial.</p> <p>1.3.2 Advise people with low back pain to exercise.</p> <p>1.3.3 Consider offering a structured exercise programme tailored to the person:</p> <ul style="list-style-type: none"> <li>• This should comprise up to a maximum of eight sessions over a period of up to 12 weeks.</li> <li>• Offer a group supervised exercise programme, in a group of up to 10 people.</li> <li>• A one-to-one supervised exercise programme may be offered if a group programme is not suitable for a particular person.</li> </ul> <p>1.3.4 Exercise programmes may include the following elements:</p> <ul style="list-style-type: none"> <li>• aerobic activity</li> <li>• movement instruction</li> <li>• muscle strengthening</li> <li>• postural control</li> <li>• stretching.</li> </ul> <p><b>1.4 Manual therapy</b></p> <p>The manual therapies reviewed were spinal manipulation (a low-amplitude, high-velocity movement at the limit of joint range that takes the joint beyond the passive range of movement), spinal mobilisation (joint movement within the normal range of motion) and massage (manual manipulation or mobilisation of soft tissues). Collectively these are all manual therapy. Mobilisation and massage are performed by a wide variety of practitioners. Manipulation can be performed by chiropractors and osteopaths, as well as by doctors and physiotherapists who have undergone specialist postgraduate training</p> |
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|  | <p>in manipulation.</p> <p>1.4.1 Consider offering a course of manual therapy, including spinal manipulation, comprising up to a maximum of nine sessions over a period of up to 12 weeks.</p> <p><b>1.5 Other non-pharmacological therapies</b></p> <p><b>Electrotherapy modalities</b></p> <p>1.5.1 Do not offer laser therapy.</p> <p>1.5.2 Do not offer interferential therapy.</p> <p>1.5.3 Do not offer therapeutic ultrasound.</p> <p><b>Transcutaneous nerve stimulation</b></p> <p>1.5.4 Do not offer transcutaneous electrical nerve simulation (TENS).</p> <p><b>Lumbar supports</b></p> <p>1.5.5 Do not offer lumbar supports.</p> <p><b>Traction</b></p> <p>1.5.6 Do not offer traction.</p> <p><b>1.6 Invasive procedures</b></p> <p>1.6.1 Consider offering a course of acupuncture needling comprising up to a maximum of 10 sessions over a period of up to 12 weeks.</p> <p>1.6.2 Do not offer injections of therapeutic substances into the back for non-specific low back pain.</p> <p><b>1.7 Combined physical and psychological treatment programme</b></p> <p>1.7.1 Consider referral for a combined physical and psychological treatment programme, comprising around 100 hours over a maximum of 8 weeks, for people who:</p> <ul style="list-style-type: none"> <li>• have received at least one less intensive treatment (see section 1.2.5) <b>and</b></li> <li>• have high disability and/or significant psychological distress.</li> </ul> <p>1.7.2 Combined physical and psychological treatment programmes should include a cognitive behavioural approach and exercise.</p> <p><b>1.8 Pharmacological therapies</b></p> <p>Both weak opioids and strong opioids are discussed in the recommendations in this section. Examples of weak opioids are codeine and dihydrocodeine (these are sometimes combined with paracetamol as co-codamol or co-dydramol, respectively). Examples of strong opioids are buprenorphine, diamorphine, fentanyl and oxycodone. Some opioids, such as tramadol, are difficult to classify because they can act like a weak or strong opioid depending on the dose used and the circumstances.</p> <p>No opioids, cyclooxygenase 2 (COX-2) inhibitors or tricyclic antidepressants and only some non-steroidal anti-inflammatory drugs (NSAIDs) have a UK marketing authorisation for treating low back pain. If a drug without a marketing authorisation for this indication is prescribed, informed consent should be obtained and documented.</p> <p>1.8.1 Advise the person to take regular paracetamol as the first medication option.</p> <p>1.8.2 When paracetamol alone provides insufficient pain relief, offer:</p> <ul style="list-style-type: none"> <li>• non-steroidal anti-inflammatory drugs (NSAIDs) <b>and/or</b></li> </ul> |
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|            | <ul style="list-style-type: none"> <li>• weak opioids<br/>Take into account the individual risk of side effects and patient preference.</li> </ul>                                                                                                                                                                                                                                                                                                        |
| 1.8.3      | Give due consideration to the risk of side effects from NSAIDs, especially in: <ul style="list-style-type: none"> <li>• older people</li> <li>• other people at increased risk of experiencing side effects.</li> </ul>                                                                                                                                                                                                                                   |
| 1.8.4      | When offering treatment with an oral NSAID/COX-2 (cyclooxygenase 2) inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either case, for people over 45 these should be co-prescribed with a PPI (proton pump inhibitor), choosing the one with the lowest acquisition cost. [This recommendation is adapted from 'Osteoarthritis: the care and management of osteoarthritis in adults' (NICE clinical guideline 59).] |
| 1.8.5      | Consider offering tricyclic antidepressants if other medications provide insufficient pain relief. Start at a low dosage and increase up to the maximum antidepressant dosage until therapeutic effect is achieved or unacceptable side effects prevent further increase.                                                                                                                                                                                 |
| 1.8.6      | Consider offering strong opioids for short-term use to people in severe pain.                                                                                                                                                                                                                                                                                                                                                                             |
| 1.8.7      | Consider referral for specialist assessment for people who may require prolonged use of strong opioids.                                                                                                                                                                                                                                                                                                                                                   |
| 1.8.8      | Give due consideration to the risk of opioid dependence and side effects for both strong and weak opioids.                                                                                                                                                                                                                                                                                                                                                |
| 1.8.9      | Base decisions on continuation of medications on individual response.                                                                                                                                                                                                                                                                                                                                                                                     |
| 1.8.10     | Do not offer selective serotonin reuptake inhibitors (SSRIs) for treating pain.                                                                                                                                                                                                                                                                                                                                                                           |
| <b>1.9</b> | <b><i>Referral for surgery</i></b>                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 1.9.1      | Consider referral for an opinion on spinal fusion for people who: <ul style="list-style-type: none"> <li>• have completed an optimal package of care, including a combined physical and psychological treatment programme (see section 1.7) <b>and</b></li> <li>• still have severe non-specific low back pain for which they would consider surgery.</li> </ul>                                                                                          |
| 1.9.2      | Offer anyone with psychological distress appropriate treatment for this before referral for an opinion on spinal fusion.                                                                                                                                                                                                                                                                                                                                  |
| 1.9.3      | Refer the patient to a specialist spinal surgical service if spinal fusion is being considered. Give due consideration to the possible risks for that patient.                                                                                                                                                                                                                                                                                            |
| 1.9.4      | Do not refer people for any of the following procedures: <ul style="list-style-type: none"> <li>• intradiscal electrothermal therapy (IDET)</li> <li>• percutaneous intradiscal radiofrequency thermocoagulation (PIRFT)</li> <li>• radiofrequency facet joint denervation.</li> </ul>                                                                                                                                                                    |

## Appendix C: Literature search for deep brain stimulation for chronic pain syndromes (excluding headache)

| 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 <i>metaRegister</i> of Controlled Trials - <i>mRCT</i>                                      | 09/03/2010    | None found                                                                                                                                                                                                                               |
| Clinicaltrials.gov                                                                                                    | 09/03/2010    | <a href="#">Evaluation of Efficacy and Safety of Deep Brain Stimulation (DBS) in Chronic and Treatment-Resistant Cluster Headache(CH)</a><br><br><a href="#">Safety Study of Deep Brain Stimulation to Manage Thalamic Pain Syndrome</a> |

Websites searched on: 09/03/2010

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) – MAUDE database

IP overview: Deep brain stimulation for chronic pain syndromes (excluding headache)

- 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.                                                        |

IP overview: Deep brain stimulation for chronic pain syndromes (excluding headache)

|    |                                                                                                              |
|----|--------------------------------------------------------------------------------------------------------------|
| 20 | Trigeminal Neuralgia/ and exp Pain, Intractable/                                                             |
| 21 | ATN.tw.                                                                                                      |
| 22 | ((trigemini* 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                                                                                                    |