DEEP BRAIN STIMULATION FOR POST STROKE PAIN

QUESTIONS TO BE ADDRESSED:

1. Is deep brain stimulation (DBS) of the periventricular grey area, sensory thalamus or alternative targets clinically effective in adults with central post-stroke pain (CPSP) refractory to analgesic medications and/or other pain treatments?

2. What is the evidence for the cost effectiveness of DBS for CPSP compared to other treatment options?

3. Does the evidence indicate whether the outcomes for DBS are affected by previous interventional treatments for CPSP?

4. Does the evidence indicate whether there is a role for DBS in sub-populations of patients with failed interventional therapies e.g. motor cortex stimulation or TMS?

SUMMARY:

Background

- Some patients who have had a stroke subsequently experience central neuropathic pain. It can lead to a burning hyperaesthesia and ache in the affected area. This may impair sleep and quality of life; it can lead to great distress.
- One treatment option is deep brain stimulation, but there is uncertainty about its clinical and cost effectiveness. Deep brain stimulation involves stereotactic targeting of specific anatomical sites in the brain to modulate the central processing of pain signals. A surgeon inserts electrodes into the brain and uses a test stimulation to check that the position is correct. Following satisfactory electrode testing, a pulse generator is implanted under the chest wall and connected by tunnelled wires to the electrodes.
- In March 2011, NICE published interventional procedures guidance on deep brain stimulation for refractory chronic pain syndromes (excluding headache). The guidance said “Current evidence on the safety of deep brain stimulation (DBS) for refractory chronic pain syndromes (excluding headache) shows that there are serious but well-known risks. There is evidence that the procedure is efficacious in some patients who are refractory to other forms of pain control. Therefore this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit.”
- NHS England does not routinely commission deep brain stimulation for chronic neuropathic pain. NHS England concluded that “there was not sufficient evidence to support the routine commissioning of this procedure for this patient group.”

Clinical Effectiveness

- We found one systematic review. It included an earlier systematic review and meta-analysis which may have been misreported and contained an important
methodological limitation. It suggested an overall success rate for DBS in CPSP of 31%. The only other studies included in this systematic review are described below.

- We found four uncontrolled studies with ten or more participants:
  - The first reported a series of 15 people with CPCP treated with DBS in Oxford. Three noticed no improvement and their electrodes were removed. The remaining twelve reported a mean improvement of 49% in their pain. Pain ratings improved by 38%. Seven participants stopped all analgesics and five others stopped regular opiates.
  - The same research group reported a series of 18 people with CPSP. Six noticed no improvement after DBS and their electrodes were removed, and three were lost to follow-up. Pain severity in the remaining nine participants showed mean improvement of 49%; the significance of this result was not reported. Four of the nine reported improvement in pain severity of at least 50%. The participants in this study may have also been reported in the first study.
  - The third study reported a series of 31 people with CPSP treated with DBS. This study was also from the same research group in Oxford and apparently included all the participants in the earlier two studies. Results were similar: four patients did not benefit from DBS and the electrodes were removed, sixteen reported an improvement in their health status and in their pain, seven had permanent electrodes but no improvement in health and the remaining four were lost to follow-up.
  - Rasche et al reported a separate set of eleven patients treated in Germany. Nine of the eleven participants experienced no pain improvement and had their electrodes removed. Patients’ quality of life did not improve because of “persistent chronic burning pain component and intermittent lancinating pain attacks.”

Cost Effectiveness
- We found no health economic evaluations of DBS for CPSP.

Safety
- Complications were not widely reported in the studies that we found. NICE’s guidance refers to the risks of intracranial haemorrhage, massive cerebral oedema and haematoma in the basal ganglia, infection, ventriculitis, subgaleal infection, subdural empyema and erosion of hardware.

1 Context

1.1 Introduction
Some patients who have had a stroke subsequently experience chronic neuropathic pain of central origin. One treatment option is deep brain stimulation, but there is uncertainty about its clinical and cost effectiveness.
1.2 Existing national policies and guidance

In March 2011, the National Institute for Health and Care Excellence published *Interventional procedures guidance on deep brain stimulation for refractory chronic pain syndromes (excluding headache).*[1] The guidance said

“Current evidence on the safety of deep brain stimulation (DBS) for refractory chronic pain syndromes (excluding headache) shows that there are serious but well-known risks. There is evidence that the procedure is efficacious in some patients who are refractory to other forms of pain control. Therefore this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit.

“During the consent process patients should be informed that DBS may not control their chronic pain symptoms. They should be fully informed about the possible risks associated with this procedure including the small risk of death.

“DBS should only be used in patients with refractory chronic pain syndromes that other treatments have failed to control. Patient selection should be carried out by a multidisciplinary team specialising in pain management.”

This guidance was from NICE’s Interventional Procedures Programme, and therefore takes into account safety and efficacy, but not cost-effectiveness. It does not constitute a recommendation that the treatment should be used, merely an indication of the circumstances in which it may be used.

In July 2015, NHS England published *Clinical commissioning policy: deep brain stimulation for chronic neuropathic pain.*[2] The policy included the treatment of central post-stroke pain (CPSP). It noted that NHS England does not routinely commission deep brain stimulation for chronic neuropathic pain. NHS England had concluded that “there was not sufficient evidence to support the routine commissioning of this procedure for this patient group.”

2 Epidemiology

The International Association for the Study of Pain Central defines central neuropathic pain as pain caused by a lesion or disease of the central somatosensory nervous system.[3] One cause of CPSP is cerebrovascular accidents, and between one and twelve percent of stroke survivors have CPSP.[4] It can lead to a burning hyperaesthesia and ache in the affected area. This may impair sleep and quality of life; it can lead to great distress.

The condition can be treated with medication but this is often not fully effective. Motor cortex stimulation is another treatment option, but such patients may also be offered DBS.
3 The intervention

DBS involves stereotactic targeting of specific anatomical sites in the brain such as the sensory thalamus or periaqueductal grey matter to modulate the central processing of pain signals. With the patient under local or general anaesthesia, a surgeon inserts electrodes into the brain under magnetic resonance and/or computed tomography imaging. A test stimulation is used to check that the position is correct. Following satisfactory electrode testing, a pulse generator is implanted under the chest wall and connected by tunnelled wires to the electrodes. Postoperative scans may be used to assess the position of the electrodes and to identify complications such as local haemorrhage.

The mechanism by which DBS works is not clear.

4 Findings

In September 2015, we searched for evidence published in the past ten years about the clinical and cost effectiveness of DBS for CPSP. The search strategy is in the Appendix. We excluded letters, commentaries, case reports and conference papers, but included all other research designs (Table 1). We also excluded two small uncontrolled studies that reported fewer than ten participants with CPSP, as they contained little additional information; they reported a further eleven patients between them.

4.1 Evidence of effectiveness

We found one systematic review (search date September 2008).[5] Its authors, Kumar et al, included an earlier systematic review of the pathophysiology and treatment on CPSP by Bittar et al.[6] However, they may have misreported Bittar et al’s analysis: Bittar et al reported the results of DBS in 45 participants with “thalamic pain (central lesion)”, but Kumar et al assume that all these had CPSP. In any case, Bittar et al’s meta-analysis had an important methodological limitation. Bittar et al report that “there was a lack of consistency between trials in the methods used to evaluate pain”, and that “no … easily quantifiable indicator was used consistently in the DBS studies”. Despite this “variability in the protocols used to evaluate a successful outcome”, they pooled each study’s reported success rate to calculate an overall success rate of 31%. This approach may mask differences in success because of differences in technique or methods of measurement.

The only other studies included by Kumar et al are described below.[7][8]

We found four uncontrolled studies with ten or more participants:[7][8][9][10]
Owen et al reported a series of 15 people with CPCP treated with DBS in Oxford.[7] Three noticed no improvement and their electrodes were removed. The remaining 12 reported a mean improvement of 49% in their pain, measured using a visual analogue scale (P < 0.001). Pain ratings on the McGill Pain Questionnaire improved by 38% (P < 0.05). Seven participants stopped all analgesics and five others stopped regular opiates.

Owen et al reported a series of 18 people with DBS.[9] Six noticed no improvement and their electrodes were removed, and three were lost to follow-up. Pain severity in the remaining nine participants showed mean improvement of 49%; the significance of this result was not reported. Four of the nine reported improvement in pain severity of at least 50%. Outcomes were “poor” in four, “fair” in two, “good” in one and “excellent” in two. It is not clear which tools were used for which results and how subjective results were defined. Some or all of the participants here may have also been reported in Owen et al[7].

Boccard et al reported a series of 31 people with CPSP treated with DBS.[10] This study was from the same research group as Owen et al and apparently included all the participants in the earlier two studies by Owen et al[7][9]. Results were similar: four patients did not benefit from DBS, seven reported an improvement in pain but not in health state and four were lost to follow-up. The remaining sixteen were reported as experiencing improvement in their health state as measured with the EQ-5D, though the changes were not significant. These participants reported a significant mean improvement of pain. Changes in other measures of pain, quality of life and health state were not significant.

There appears to be a high degree of overlap between the participants reported in Owen et al[7], Owen et al[9] and Boccard et al[10].

Rasche et al reported a separate set of patients, treated in Lübeck, Germany, eleven of whom had CPSP.[8] Whereas the Oxford group proceeded to full electrode implantation in patients who reported an improvement in symptoms, Rasche et al required an improvement of at least 50%, measured using visual analogue scale by patient, physician and nurse during double-blind testing, along with a marked reduction in analgesic medications and an increase in activities of daily living. No narcotic medications were used during the week between surgery and testing, with opioids withdrawn pre-operatively in some cases. Nine of the eleven participants experienced no pain improvement and had their electrodes removed, and a tenth only had pain relief of 25% to 50%, though he proceeded to permanent implantation nonetheless, for unreported reasons. The final patient had pain relief of 50% to 75%. Describing these results as “very disappointing”, Rasche et al note that “Although some beneficial effects on allodynia … were observed, this did not increase the patients’ quality of life because of persistent chronic burning pain component and intermittent lancinating pain attacks.”
4.2 Trials in progress
We searched clinicaltrials.gov but found no studies in progress of DBS for CPSP.

4.3 Evidence of cost-effectiveness
We found no health economic evaluations of DBS for CPSP.

4.4 Safety
Complications were not widely reported in the studies that we found. NICE’s guidance refers to the risks of intracranial haemorrhage, massive cerebral oedema and haematoma in the basal ganglia, infection, ventriculitis, subgaleal infection, subdural empyema and erosion of hardware.

4.5 Summary of section 4
We found no studies comparing the effectiveness of DBS for CPSP with any other treatment. The uncontrolled studies that we found reported a total of only 42 people, assuming that Boccard et al reported all the participants in Owen et al[7] and Owen et al[9], previous publications from the same research group. The evidence suggests that in some patients DBS can produce an improvement in symptoms; this may be as many as half according to one set of results, though the more stringent criteria used elsewhere suggest that meaningful improvements are much less common. No increase in quality of life has been reported, and impact on activities of daily living and cognitive ability has not been investigated.

The procedure carries a risk of serious side effects. Its cost effectiveness is unknown. The effects, where observed, appear to persist for at least two years.
### Table 1: Studies of deep brain stimulation for central post-stroke pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Owen et al [7]</td>
<td>15 people with stroke (5 cortical, 8 thalamic, 1 pontine, 1 internal capsule) and CPSP</td>
<td>Deep brain stimulation</td>
<td>Uncontrolled</td>
<td>3/15 (20%) participants noticed no improvement and their electrodes were removed.</td>
<td>It is not clear what treatments participants had previously received and whether they met the inclusion criteria for this review.</td>
</tr>
<tr>
<td></td>
<td>Mean age 59 years, mean duration of pain 5 years.</td>
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<td></td>
<td>The remaining 12 reported a mean 49% improvement on pain VAS (P &lt; 0.001). MPQ pain rating reduced by 38% (P &lt; 0.05).</td>
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<td>Large variation in MPQ results, from 2% deterioration to 91% improvement.</td>
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<td>7/12 participants stopped all analgesics and 5 stopped regular opiates.</td>
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<td>Average follow-up 27 months.</td>
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<tr>
<td>Owen et al [9]</td>
<td>18 people with stroke and CPSP, part of a larger group of 47 having DBS for various indications.</td>
<td>Deep brain stimulation</td>
<td>Uncontrolled</td>
<td>6/18 (33%) participants noticed no improvement and their electrodes were removed.</td>
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<td></td>
<td>Mean age of all CPSP participants 50</td>
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<td>3/12 (25%) participants had no follow-up data.</td>
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<td>Pain severity in the 9 participants implanted and followed up: mean improvement 49% (significance not reported). 4/9 (44%) reported</td>
<td>Participants were refractory to conventional management.</td>
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<td></td>
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<td>Results measured with VAS and MPQ. It is not clear which tools were used for which results and how subjective results were defined.</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>Boccard et al [10] Oxford, UK</td>
<td>31 people with stroke and CPSP, part of a larger group of 85 having DBS for various indications. Mean age of all CPSP participants 59 years.</td>
<td>Deep brain stimulation</td>
<td>Uncontrolled</td>
<td>4/31 (13%) participants noticed no improvement and their electrodes were removed. 4/31 (13%) participants had no follow-up data. 16/31 (52%) were reported as experiencing improvement in their health state as measured with the EQ-5D, though the changes were not significant (P = 0.514). These participants reported a mean improvement of pain measured with VAS of 38%, P &lt; 0.001. The changes in MPQ (P = 0.191), SF-36 (P = 0.374), and health state (P = 0.291) were not significant.</td>
<td>Mean follow-up 45 months. The participants here may have also been reported in Owen et al[7]. Participants were refractory to conventional management. The participants here were also reported in Owen et al[7] and Owen et al[9]. Participants’ response to DBS was tested single-blind, but there were no explicit criteria for implantation.</td>
</tr>
<tr>
<td>Rasche et al [8] Lübeck, Germany</td>
<td>11 people with stroke and CPSP, part of a larger group of 56 having DBS</td>
<td>Deep brain stimulation</td>
<td>Uncontrolled</td>
<td>9 of 11 experienced no pain improvement and their electrodes were removed as a consequence. One of the remaining participants reported improvement of 50% to</td>
<td>Participants were refractory to conventional management.</td>
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</table>
### Study Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
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<td></td>
<td>for various indications. Mean age of these 11 people: 59 years</td>
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<td>75%, and the other improvement of 25% to 50%. These participants were followed-up for 1 and 2.5 years respectively.</td>
<td>It is not clear why the second participant’s electrodes were not removed, as the trial protocol required in participants whose symptoms did not improve by at least 50%.</td>
</tr>
</tbody>
</table>

EQ-5D: EuroQoL-5D quality of life questionnaire. MPQ: McGill pain questionnaire. VAS: visual analogue scale
5 Discussion and conclusions

The evidence in support of DBS is scanty. There are no controlled studies. It is hard to be certain how many participants there were in the studies we included because of overlap, but it is probably no more than forty-two, with another eleven in the small studies we excluded.

There are reports of improvements in pain, but only in a proportion of patients – perhaps around half, though there is too little evidence to be precise. This improvement, even if it occurs, does not appear to improve quality of life; whether it is cost effective is unknown. How much is due to placebo effects is uncertain: when more rigorous criteria were used to decide whether to implant electrodes permanently, including double-blind testing of efficacy, nearly all patients reported no effect from DBS on their CPSP.[8]

Impact on activities of daily living and cognitive ability has not been investigated.

1. Is deep brain stimulation (DBS) of the periventricular grey area, sensory thalamus or alternative targets clinically effective in adults with central post-stroke pain (CPSP) refractory to analgesic medications and/or other pain treatments?

Evidence relevant to this question is limited to four uncontrolled studies of low methodological quality. Sometimes DBS is followed by improvements in pain in people with CPSP refractory to medication. However, the evidence suggests that there is no improvement in quality of life. The clinical significance of the reduction in pain is not reported, and there is no evidence about improvements in activities of daily living.

2. What is the evidence for the cost effectiveness of DBS for CPSP compared to other treatment options?

We found no health economic evaluations of DBS for CPSP.

3. Does the evidence indicate that the outcomes for DBS are affected by whether or not patients have had prior interventional treatments for their pain?

We found no evidence relevant to this question. There appear not to be any studies which have examined whether previous interventions influence the results of DBS for CPSP.

4. Does the evidence indicate that there is a role for DBS in sub-populations of patients with failed interventional therapies e.g. motor cortex stimulation or TMS?
We found no evidence relevant to this question. There appear not to be any studies which have examined whether the results of DBS for CPSP are different in people with previous unsuccessful invasive treatment.

**Competing Interest**
All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from NHS England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years: no other relationships or activities that could appear to have influenced the submitted work

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6 References


### 7 Search Strategy

Population, Intervention, Comparator and Outcomes (PICO)

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults age 18+, diagnosed as having central post-stroke pain (CPSP) refractory to analgesic medications and other pain treatments</td>
<td>Deep Brain Stimulation Major targets:  - Periventricular grey area  - Thalamus: nuclei including the ventralis caudalis; ventral posterior lateral; ventral posterior medial nuclei. Additional thalamic targets may be described Alternative targets:  - Spinothalamocortical tract at the level of the posterior limb of the internal capsule  - Nucleus accumbens  - Anterior cingulate cortex</td>
<td>Ongoing analgesic medication on Motor cortex stimulation on Transcranial magnetic stimulation on Intrathecal Drug Delivery (ITDD) non cancer pain</td>
<td>Clinical effectiveness including:  - Reduction in pain intensity based on pain evaluation tools such as visual analog score or McGill Pain Questionnaire  - Change in analgesic medication intake per 24 hours  - Functional ability, including cognitive ability  - Quality of life measured by SF-36, EuroQOL or other valid measure of quality of life  - Short and long term adverse events including:  - Neuropsychological deterioration.  - Skin erosion  - Infection  - Haemorrhage  - Subdural</td>
<td>Meta-analyses Systematic reviews Randomised controlled trials Prospective non-randomised clinical study Other clinical study Health economics studies Case studies Date limits Search for evidence published since 2005</td>
</tr>
</tbody>
</table>
EVIDENCE SUMMARY REPORT

14

haemorrhage
  o Status epilepticus
  o Death, including SUDEP
  o New or worsening seizures

Safety and adverse events including:
  Safety of surgery
  Safety of implanted device
  Cost effectiveness

Search date: 21 September 2015
Databases searched: on Medline, Embase, Cochrane, TRIP and NICE Evidence Search, limited to the past 10 years. We excluded letters, commentary, case reports and conference papers.

Embase Strategy

1 exp cerebrovascular accident/
2 (stroke or post-stroke or poststroke).ti,ab.
3 ((brain or cerebral or intracerebral or intra-cerebral or cerebrovascular or cerebrovascular or hemisphere) adj2 (infarct* or accident?!)).ti,ab.
4 1 or 2 or 3
5 pain.mp.
6 4 and 5
7 ((thalamic or thalamus) adj2 pain).ti,ab.
8 6 or 7
9 brain depth stimulation/
10 (deep brain stimulat* or dbs).ti,ab.
11 ((brain or cerebral or intracerebral or intra-cerebral or cerebrovascular or cerebrovascular or thalamic or thalamus) and electric* and (stimulat* or neurostimulat*))).ti,ab.
12  ((brain or cerebral or intracerebral or intra-cerebral or cerebrovascular or cerebrovascular or thalamic or thalamus) adj3 (pacemaker? or neurostimulat*)).ti,ab.

13  9 or 10 or 11 or 12

14  8 and 13

15  limit 14 to english language