Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Occipital nerve stimulation for treating medically refractory chronic cluster headache

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: is occipital nerve stimulation clinically and cost effective in comparison to standard care in people with medically refractory chronic cluster headaches?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of identifying published evidence on the best clinical and health economic evidence on health technologies. This report includes an adapted 'hotline response' report from the ECRI Institute's Health Technology Assessment Information Service. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales (HTW) multidisciplinary advisory groups before publication.

2. Health problem

Chronic cluster headache is a rare but severe primary headache disorder for which the pathophysiology and aetiology are not well understood (Fuller&Kaye 2007). 'Cluster' refers to a group of headaches that occur over several weeks. The chronic condition is characterised by:

- attacks of severe or very severe, strictly unilateral (one-sided) pain that typically occur every other day, every day, or even several times a day and last 15 minutes to three hours.
- attacks occurring for more than one year without remission, or where the remission period is less than one month (NICE 2017).
- symptoms such as lacrimation, nasal congestion, forehead and facial sweating or eyelid swelling (NICE 2017).

Cluster headache affects 69 in 100,000 people in the UK (Fuller&Kaye 2007) and about 15-20% of people with cluster headaches suffer from chronic cluster headaches (Láinez&Guillamón 2017). Men are more likely to suffer from cluster headache than women. However, expert opinion advises that this difference is largely due to historical misdiagnoses in the female population and it is thought that awareness and diagnosis of chronic cluster headache is improving.

Between 5% and 20% of people with chronic cluster headaches develop medically refractory headaches that do not respond to treatment and continue to have daily or almost-daily attacks for long periods of time (Mueller et al. 2013, Láinez&Guillamón 2017, Leone et al. 2017). Using these prevalence rates, we estimate that there are between 16 and 65 people in Wales with

medically refractory chronic cluster headaches; expert opinion suggests that this estimate may be conservative.

Treatment approaches for chronic cluster headache management include strategies to stop the acute symptoms during headache attacks (short-burst oxygen therapy, subcutaneous or nasal triptans) and preventive strategies (preventative medication, avoiding triggers). For medically refractory cases, both invasive and non-invasive surgical treatment has been used.

3. Health technology

Occipital nerve stimulation uses an implantable system consisting of a pulse generator and electrodes to stimulate the greater and lesser occipital nerves. The mechanism of action is poorly understood, but may involve activation of large myelinated afferent nerves and inhibition of pain signals in the substantia gelatinosa located in the spinal cord.

A healthcare professional implants the electrode lead in subcutaneous tissue supplied by the greater and lesser occipital nerves and implants the battery-operated pulse generator in a subcutaneous pouch in the chest, abdomen, or back.

Currently, ONS hardware is available from Abbot (formally St Jude Medical), Medtronic and Boston Scientific.

4. Current guidelines and guidance

A position statement on neuromodulation of chronic headaches from the European Headache Federation (2013) states that occipital nerve stimulation is an “invasive, expensive and probably non-specific technique that must be employed with caution and only carefully considered for the most severely affected patients with medically refractive chronic cluster headache” (Martelletti et al. 2013).

A more recent guideline on the treatment of cluster headache from The American Headache Society (2016) did not include occipital nerve stimulation in their review due to the lack of randomised controlled trials (Robbins et al. 2016). They further state that “as invasive neurostimulation carries inherent risks of serious adverse events, these therapies should largely be reserved for further clinical trials or where patients with chronic cluster headache have truly failed a multitude of other preventative therapies. However, the threshold to utilise non-invasive neurostimulation would presumably be much lower, though evidence at this time is limited and comparative studies to medication therapies are not yet available.” (Robbins et al. 2016).

In 2015, NHS England produced a clinical commissioning policy for occipital nerve stimulation for adults with chronic migraine and medically refractory chronic cluster headaches (NHS England 2015). The policy concluded that medically refractory chronic cluster headache is a highly disabling condition, and occipital nerve stimulation is considered to be an effective option for people whose headaches are refractory to other available therapies.

The National Institute for Health and Care Excellence (NICE) have medical technologies guidance in development for gammaCore, a non-invasive vagus nerve stimulator, for cluster headaches (NICE 2019) . The draft guidance recommends that “evidence supports the case for adopting gammaCore to treat cluster headache in the NHS”. It also recommends that gammaCore treatment should only continue if symptoms have improved during a 3-month trial. The expected publication date for the final guidance is December 2019.

5. Evidence search methods

The Population-Intervention-Comparator-Outcomes (PICO) framework for the evidence appraisal (Appendix 1) was developed following comments from the HTW Assessment Group and UK experts. The framework was then shared with the ECRI Health Technology Assessment Information service (www.ecri.org), who were commissioned by HTW to produce a report on this technology.

ECRI searched PubMed, EMBASE, the Cochrane Library, and selected web-based resources for documents published between 1 January 2009 and 17 July 2019. Their search strategies included the following keywords: "cluster headache" AND "occipital nerve stimulation". For completeness, HTW carried out additional searches to cover dates not searched by ECRI, in addition to searching websites that were not included in the ECRI report. Further details on the ECRI and HTW search strategies are available on request to HTW.

Identified studies were only included if outcomes were reported for people with medically refractory chronic cluster headache specifically, i.e. not only reported as a population with different conditions. Patient safety and organisational issues were identified from the papers included in the clinical effectiveness section and expert advice; no specific searches were undertaken. Appendix 2 summarises the selection of articles for inclusion in the review.

6. Clinical effectiveness

We did not identify any randomised controlled trials for occipital nerve stimulation in medically refractory chronic cluster headache, with the exception of one recently concluded study (see Section 5.4). All the published studies were either prospective or retrospective case series.

Two systematic reviews were identified that reported occipital nerve stimulation for chronic cluster headache. The first review aimed to provide a comprehensive summary of peripheral nervous system-targeted therapeutic strategies in patients with refractory primary headache disorders (Tajti et al. 2019). The earliest study date considered for inclusion in the review was January 2012; the authors did not report a reason for this date limitation. It reported five case series for occipital nerve stimulation for medically refractory chronic cluster headaches. However, on assessment, one study appeared to be incorrectly referenced within the review, as it looked at other primary headache disorders and not chronic cluster headaches alone (Miller et al. 2018). Another of the studies was a narrative review that reported data attributed to a conference abstract (Láinez&Guillamón 2017). These two studies were therefore excluded from this report. Study characteristics for the remaining three studies are detailed in Table 1 (Fontaine et al. 2017, Leone et al. 2017, Mueller et al. 2013).

The second systematic review aimed to evaluate whether occipital nerve stimulation is an effective treatment for benign headache (Jasper&Hayek 2008). Three studies for chronic cluster headache were identified. One of these studies was excluded from this review as it included multiple primary headache disorders and did not report data for chronic cluster headache separately (Schwedt et al. 2007). Burns et al. (2007) was not included in this review as our searches identified a more recent follow-up report with additional patients (Burns et al. 2009). Details for the remaining included study are reported in Table 1 (Magis et al. 2007).

Additional primary studies were identified. One study investigated occipital nerve stimulation in primary headache disorders, but it did not report relevant outcomes for chronic cluster headache separately and was therefore excluded (Brewer et al. 2012). One study reported a follow-up for Burns et al. (2007). Different outcomes from a specific cohort were reported in each published

follow-up, so the most recent data was reported for each outcome where possible (Magis et al. 2016, Burns et al. 2009, Magis et al. 2011).

6.1. Clinical outcomes

Table 2 summarises the clinical outcomes for occipital nerve stimulation in people with medically refractory chronic cluster headaches. For the cohort reported through Magis et al. (2011), only the most recently reported data for that outcome is included.

Following the introduction of occipital nerve stimulation, people with medically refractory chronic cluster headache saw a decrease in attack frequency; a significant reduction was reported in four out of five studies (Leone et al. 2017, Fontaine et al. 2017, Miller et al. 2017, Magis et al. 2011). According to four studies, people who experienced more than 50% improvement in symptoms, defined as more than 50% reduction in headache attacks, ranged between 53% and 90%, (Leone et al. 2017, Fontaine et al. 2017, Miller et al. 2017, Magis et al. 2016).

Results showing change in attack severity were more varied. Two studies showed significant reduction in both attack intensity and duration (Fontaine et al. 2017, Miller et al. 2017), whereas another study showed no improvement in attack intensity (Magis et al. 2011). However, Magis et al. (2011) did report that 64% (9/14) patients were pain free. Miller et al. (2017) also reported that 47% (24/51) patients were pain-free for more than 6 months. The study by (Burns et al. 2009)Burns et al. (2009) reported that no people with medically refractory chronic cluster headaches were pain free, but 71% (10/14) noted improvement in their condition.

Few studies reported changes in preventative treatment. Following occipital nerve stimulation, two studies reported a reduction and/or complete halting of preventative treatment in 40% and 78% of people with medically refractory chronic cluster headache, respectively (Fontaine et al. 2017, Miller et al. 2017). However, one of these studies also noted that some people (18%) increased preventative treatment (Fontaine et al. 2017). The third study reported that all people maintained preventative treatment (Leone et al. 2017).

6.2. Quality of life outcomes

We identified two studies that measured changes in quality of life (Fontaine et al. 2017, Miller et al. 2017). The studies used various tools to measure quality of life:

- Migraine disability assessment score (MIDAS)
- Headache Impact Test 6 (HIT-6)
- EuroQol 5 Dimension (EQ-5D) index and EQ-5D visual analogue scale (VAS)
- Short Form 36 questionnaires (SF-36)
- Hospital anxiety and hospital depression scores – anxiety (HAD-A) and depression (HAD-D) components
- Beck depression inventory II (BDI-II)
- Patients Global impression of change (PGIC)

Quality of life outcomes are presented in Table 3. Significant improvement was reported for MIDAS, HIT-6, HAD-A, HAD-D and BDI-II scores ($p<0.02$ for all analyses). Fontaine et al. (2017) reported significant improvement through the EQ-5D and EQ-5D VAS tools ($p = 0.0013$ and $p = 0.0037$, respectively); however, this change was not observed in the Miller et al. (2017) study ($p = 1.00$ and $p = 0.285$, respectively). Miller et al. (2017) also used SF-36 and showed no improvement in the physical component ($p = 0.191$) but did show improvement in the mental component ($p = 0.036$). Self-reported improvement through the PGIC score showed that 55.4% of people felt that their condition was improved or very improved after occipital nerve stimulation.

Table 1: Study characteristics

Study	Study design	Participants	Intervention	Outcomes	Comments
Tajti (2019), systematic review					
Leone (2017)	Open-label single centre, long-term. Median follow-up 6.1 years (range 1.6 to 10.7 years) Single centre, Italy	Inclusion criteria: people aged 18–70 years with chronic cluster headache (according to International Headache Society criteria); daily/almost daily attacks in the last year; resistance to all known preventative drugs for cluster headache. Mean age: 42 years Sex: 86% male; 14% female Illness duration: 6.7 years	Unilateral or bilateral ONS.	• Number of daily attacks (primary outcome) • ≥50% reduction in headache number per day (responder) • Change in steroid use • Change in preventative use • Adverse events	
Fontaine (2017)	Observational prospective case series. Data was prospectively collected before surgery, 3 months post-surgery and 12 months post-surgery. Multicentre (n = 10), France	Inclusion criteria: diagnosis of chronic cluster headache; duration of over three years; daily attacks; resistance to more than two pharmacological preventative treatments with adequate trials. Patients were from the French database of ONS for the treatment of refractory chronic headache disorders, a prospective database for chronic headache patients undergoing ONS. Included patients had ONS with at least one year follow-up.	Bilateral ONS	• Weekly attack frequency • Mean attack duration (minutes) • Mean attack intensity (scales 0 to 10) • Medication related to cluster headache (e.g. preventatives) • Functional impact, using the short version of the Headache Impact Test (HIT-6) • Emotional impact using the Hospital Anxiety and	

Study	Study design	Participants	Intervention	Outcomes	Comments
				Depression Scale (HAD-A and HAD-D). • Disability using the Migraine Disability Assessment (MIDAS) • Health-related quality of life using the EQ-5D-3L • Patients Global Impression of Change (PGIC)	
Mueller (2013)	Prospective observational long-term case series. Mean follow-up was 20 months (range 5 to 47 months) Single centre, Germany	People with chronic cluster headache (n = 24) or chronic migraine (n = 3). Refractory chronic cluster headache was defined as: • daily attacks without attack-free periods for more than four weeks per year despite preventative medication, or • if side effects of the preventative or acute medication impeded sufficient control of attacks. Mean age: 30 years Sex: 66.7% male; 33.3% female	Bilateral ONS.	• Percentage of responders • Attack frequency • Relief of pain intensity on a scale 0 to 10.	
Jasper (2008) systematic review					
Magis (2007)	Prospective case series Mean follow-up 15.1 months, range 3 to 22 months.	Inclusion criteria: patients who had chronic cluster headache for at least two years; four or more attacks per week; side-locked attacks from the beginning of the disease; no associated disabling	Unilateral ONS.	• Attack frequency • Attack intensity • Adverse events	The location of the study is not described; it is possibly a single-centre cohort in

Study	Study design	Participants	Intervention	Outcomes	Comments
		organic or psychiatric disorder; resistant to drug treatment. Mean age: 45.3 years (SD 9.7 years) Sex: 87.5% male (7/8 patients)			Belgium (author location).
Other studies					
Miller (2017)	Prospective long-term study. Mean follow-up 39 months (range 2 to 81 months) Single centre, UK.	Inclusion criteria: Patients with intractable chronic cluster headache that had failed at least four treatments. Mean age: 47.8 years (range 31 to 70 years). Sex: 68.6% male; 31.4% females 19 patients (37.3%) had other chronic headaches in addition to CCH: • 13 had CCH and CM • 3 had CCH and SUNHAs • 3 had CCH, CM and SUNHA.	Bilateral ONS.	• Improvement in mean daily attack frequency • Responders, defined as a 50% or more reduction in mean daily attack frequency • Attack severity and duration • Headache-related disability scores • Quality of life scores.	
Magis (2016)	Prospective case series, long-term follow-up Mean follow-up 71 months (range 54 to 103).	Inclusion criteria: people with drug resistant chronic cluster headaches; side-locked attacks. Six patients had been chronic from the outset. Mean age 47.6 years (SD 9.6 years) Sex: 93% male; 7% females Duration of chronic phase: 7 years (SD 4.2 years).	Unilateral ONS.	• Long-term change in condition • >50% decrease in attack frequency • Adverse events / discontinuations	Most recent long-term follow-up from Magis (2007) and Magis (2011).
Magis (2011)	Prospective case series, long-term follow-up	Inclusion criteria: people with drug resistant chronic cluster headaches; side-	Unilateral ONS.	• Attack frequency • >50% reduction in attack frequency	Follow-up from Magis (2007).

Study	Study design	Participants	Intervention	Outcomes	Comments
	Mean follow-up 36.8 months (range 11 to 64 months)	locked attacks. 6 patients had been chronic from the outset. Mean age 47.6 years (SD 11.5 years) Sex: 93% male (14/15 patients) Duration of chronic phase seven years (SD 4.2 years).		• Adverse events	
Burns (2009)	Retrospective case series. Median follow-up 17.5 months (range 4 to 35 months). Single centre, UK	Inclusion criteria: people with medically refractory chronic cluster headache.	Bilateral ONS; one patient began with unilateral ONS and had the second implant nine months later. Patients were provided with remote controls to adjust the stimulator settings.	• Attack frequency • Attack severity • Attack duration • Patient perceptions • Adverse events	Follow-up from Burns (2007). "Patients were implanted on compassionate grounds and the study was an audit of outcome and, as such under UK guidelines, does not require ethics committee approval." (Burns, 2009) The majority of outcomes were reported for each individual patient, and therefore could not be included here.
CCH: chronic cluster headache; CM: chronic migraine; ONS: occipital nerve stimulation; SUNHA: short-lasting unilateral neuralgiform headache attacks.					

Table 2: Occipital nerve stimulation – clinical outcomes

Study	Participants	Outcome	Comments
Attack frequency			
Leone (2017)	30	Reduction from 5.7 to 2.4 per day (p<0.001) per day	
Fontaine (2017)	44 at 12 month follow-up	Reduction from 21.53 (SD 16.25) to 10.65 (SD 13.78) per week (p = 0.0002)	
Miller (2017)	51	Reduction from 3.73 (SD 1.83) to 2.12 (SD 2.28; p<0.0001) per day	Data includes 19 patients with CCH as well as other primary headache conditions (see Table 1). Subgroup data was presented for CCH alone and showed the same trend in reduction of attack frequency.
Mueller (2013)	24	Reduction from five attacks (range 1 to 14 per day) to three attacks per day (range 0 to 8 per day)	Statistical analysis of data not provided.
Magis (2011)	14	Reduction from 2.24 to 0.12 (p = 0.001) per day.	
>50% improvement (reduction in attack frequency)			
Leone (2017)	30	66.7% (20/30)	
Fontaine (2017)	44 at 12 month follow-up	59% (26/44)	64% had improvement >30%
Miller (2017)	51	52.9% (27/51)	
Magis (2016)	10	90% (9/10)	
Attack severity			
Fontaine (2017)	28 at 12 month follow-up	Attack intensity reduced from 8.29 (SD 1.80) to 7.46 (SD 2.35; p = 0.0427) Attack duration reduced from 53.67 minutes (SD 52.89) to 38.15 minutes (SD 37.64; p = 0.0131)	Attack intensity was based on a numeric scale from 0 to 10.
Miller (2017)	51	Attack intensity reduced from 8.43 (SD 1.61) to 6.17 (SD 3.54; p<0.0001) Attack duration reduced from 1.66 hours (SD 1.62) to 0.85 (SD 0.98; p<0.0001) 47% (24/51 patients) reported >6 months freedom from pain	Data includes 19 patients with CCH as well as other primary headache conditions (see Table 1). Subgroup data was presented for CCH alone

Study	Participants	Outcome	Comments
			and showed the same trend in results.
Mueller (2013)	44 at 12 month follow-up	Mean pain score reduced from 8 to 5.	Statistical analysis not reported.
Magis (2011)	14	Mean intensity of residual attacks is not improved (p>0.05) 64% (9/14 patients) reported as pain-free	
Burns (2009)	14	71% (10/14 people) noted improvement in their condition (self-reported). 0were pain-free	
Reduction in preventative treatment			
Leone (2017)	30	All subjects maintained preventative treatment	
Fontaine (2017)	50 at 12 months follow-up	20 subjects(40%) decreased preventative treatments (18% increased preventative treatment)	
Miller (2017)	27	15% (4/27) stopped preventative treatment. 63% (17/27) reduced preventative treatments	
CCH: chronic cluster headache; SD: standard deviation.			

Table 3: Occipital nerve stimulation – quality of life

Study	Participants	Quality of life outcome	Comments
MIDAS			
Fontaine (2017)	33	At baseline 100% patients were grade IV. At 12 month follow-up, 68.75% were still grade IV, but one patient (3.12%) reported grade II and nine patients (28.13%) reported grade I (no disability); p = 0.0020.	MIDAS score had not been validated in CCH, but has been used for other primary headache disorders (including other cluster headaches). MIDAS grades: 0 to 5 - grade I, no disability; 6 to 10 - grade II, some disability; 11 to 20 - grade III, significant disability; >21 - grade IV, severe disability)
Miller (2017)	51	Mean score reduced from 149.84 (SD 89.10) to 114.92 (SD 106.66; p = 0.016)	
HIT-6			
Fontaine (2017)	35	Reduction from 67.77 (SD 5.42) to 61.37 (SD 10.96; p = 0.0002)	A HIT-6 score over 60 is considered very severe impact. It is worth noting that HIT-6 score reduced to 55.24 at 3 months, before rising again.
Miller (2017)	51	Reduction from 67.73 (SD 6.08) to 60.68 (SD 13.07; p<0.001)	
EQ-5D			
Fontaine (2017)	33	Increased from 0.38 (SD 0.14) to 0.55 (SD 0.26; p = 0.0013)	
Miller (2017)	49	No change in score 0.69 (SD 0.11) to 0.69 (SD 0.15; p = 1.00)	
EQ-5D VAS			
Fontaine (2017)	33	Increased from 35.15 (SD 23.57) to 51.85 (SD 25.70; p = 0.0037)	
Miller (2017)	49	Score increases from 49.75 (SD 23.24) to 52.42 (SD 27.62; p = 0.285)	

Study	Participants	Quality of life outcome	Comments
SF-36			
Miller (2017)	51	**SF-36 P** Score does not change significantly 32.12 (SD 9.97) to 33.82 (SD 11.80; p = 0.191) **SF-36 M** Score increases from 34.14 (SD 12.97) to 38.34 (SD 14.79; p = 0.036)	
HAD-D			
Fontaine (2017)	35	Reduction from 11.91 (SD 3.94) to 7.49 (SD 4.73; p<0.0001)	Anxiety and depression impairment is considered with subscores >7.
Miller (2017)	51	Reduction from 12.04 (SD 4.68) to 9.22 (SD 6.10; p = 0.001)	
HAD-A			
Fontaine (2017)	35	Reduction from 11.91 (SD 3.94) to 10.06 (SD 4.27, p<0.0001)	Anxiety and depression impairment is considered with subscores >7 .
Miller (2017)	51	Reduction from 12.16 (SD 5.005) to 10.12 (SD 5.41; p= 0.013)	
BDI-II			
Miller (2017)	49	Mean score reduced from 27.59 (SD 14.45) to 22.82 (SD 15.98; p = 0.018)	
PGIC			
Fontaine (2017)	47	55.4% of patients reported as very improved or improved	The author noted PGIC scores for very improved/improved decreased between the 3 and 12 month time points (77% at 3 months).

Note: Data for Miller (2017) includes 19 people with CCH as well as other primary headache conditions (see Table 1). Subgroup data for CCH alone showed similar results, with the exception that the change in SF-36 M score was not statistically significant.
BDI-II: Beck depression inventory II; EQ-5D: EuroQol 5 dimension index; EQ-5D VAS: EuroQol 5 dimension visual analogue scale; HAD-A: hospital anxiety and depression scale (anxiety); HAD-D: hospital anxiety and depression scale (depression); HIT-6: headache impact test; MIDAS: migraine disability assessment; PGIC: patient's global impression of change; SF-36: short form 36 questionnaire.

6.3. Safety

All six studies reported adverse events, which are detailed in Table 4. Reported adverse events included battery replacement, battery depletion (either early or expected), stimulation issues, electrode or lead displacement, contralateral attacks, discomfort and/or pain at surgery sites, neck stiffness and infection. Reasons for explantation included infection (immediate and delayed), lack of efficacy and intolerance of paraesthesia.

Induction of paraesthesia through occipital nerve stimulation is a necessary effect for treatment. In some cases, intolerance resulted in altering the stimulation (changing amplitude, intermittent frequency). Two people in one study explanted due to unbearable paraesthesia. Overall, the paraesthesia appeared to be tolerated by the majority of patients.

6.4. Ongoing studies

We identified one ongoing study (the ICON study) that aimed to investigate efficacy of occipital nerve stimulation for people with medically refractory chronic cluster headaches. This study is a multicentre (Belgium, Germany, Hungary, Netherlands), double-blind, randomised controlled trial (NCT01151631 2018). The study compares occipital nerve stimulation to sham (30% stimulation). The estimated final completion date for this study was March 2019.

One protocol was identified on the PROSPERO database, outlining a systematic review that aims to evaluate the efficacy and safety of occipital nerve stimulation compared to the best available medical treatment or sham stimulation for patients suffering from chronic headaches, excluding migraines (Cottin et al. 2019). The protocol states that the authors of pertinent trials will be contacted concerning upcoming publications. Estimated completion date for this systematic review was September 2019.

Table 4: Occipital nerve stimulation - safety

Study	Participants	Adverse events	Comments
Leone (2017)	35	32 AEs reported in 23 people and included: battery depletion (65.6%, 21 people); electrode migration (18.8%, 6 people); electrode malfunction (3.1%, 1 person); electrode decubitus (3.1%, 1 person); wire decubitus (6.3%, 2 people); wire malfunction (3.1%, 1 person) 9 people experienced unbearable paraesthesia and required amplitude adjustment for a brief period (but none ended ONS).	The author noted that in the cases of battery depletion, symptoms worsened, but then improved after battery change.
Fontaine (2017)	58	19 people (33%) had at least 1 surgical complication at 1-year follow-up: hardware infection (1 person), wound issue (1 person), electrode migration (2 people), hardware-related discomfort (2 people), hardware/simulation dysfunction (9 people), early battery depletion (8 people). 15 (26%) people required additional surgery, including 8 battery replacements; reason for surgery for the other 7 people was not reported. Paraesthesia was well tolerated in all cases. 2 were explanted before the 12 month follow-up due to lack of efficacy.	
Miller (2017)	51	81 AEs recorded in total: 38 hardware-related, 26 biological-related, 17 stimulator-associated. 38 events required surgical intervention. Most common AEs included battery replacement (19 people, 6 of which were due to battery depletion), undesirable changes in stimulation (17 people), pain over wound sites (12 people, 2 of which required reoperation), neck stiffness (8 people), ONS system revision (6 people), lead migration (1 person), erosion of electrodes through the skin (2 people), infection (1 person). Explantation occurred in 4 people (7.8%).	Intolerance to paraesthesia was not reported; electrodes were adjusted at follow-up visits to ensure comfortable bilateral paraesthesia.
Mueller (2013)	27	5 non-hardware complications were reported: infection (6 people, 5 of which required reoperation); worsening cluster attacks (2 people); loss of effectiveness (1 person); nausea (1 person) and pressure ulcers at operation site (1 person).	Note that the safety population included 3 people with chronic migraine. Tolerance to paraesthesia was not reported.

Study	Participants	Adverse events	Comments
		Four hardware complications: Local pain/discomfort (4 people, 3 required reoperation), cable breaks (3 people, all three required reoperation), lead dislocation (1 patient), IPG discharge (2 people, both required reoperation). 4 people (15%) explanted due to local infection.	
Burns (2009)	14	Most common complication was battery depletion and replacement in 6/14 people (43%). 4/14 (29%) required new electrodes/leads. Muscle contraction, neck stiffness, skin discomfort, superficial infections, and painful overstimulation were also reported. 1 person resorted to intermittent stimulation due to paraesthesia.	
Magis (2007)	8	No serious adverse effects reported. 1 person explanted 12 months after surgery, 2 people experienced contralateral attacks (resolved after steroid injections), 4 people needed battery replacements, 1 person had lead displacement, 1 person had electrode displacement following a fall (surgical revision planned); 1 stimulator switched off due to external interference. 7/8 people adapted to the paraesthesia.	
Magis (2011)	15 (14 included in safety population)	1 person was excluded from the study due to infection 15 days post-surgery, resulting in explant. Reported AEs were: battery depletion (64%, 9 patients); contralateral attacks (36%, 5 people); isolated ipsilateral autonomic attacks without pain (36%, 5 people); delayed infection (13%, 2 people); significant electrode migration (7%, 1 person). 72% (8/11) people with an improved condition reported recurrence or increase in frequency of attacks after stimulation arrest. 2 people reported unbearable paraesthesia	
Magis (2016)	15 (10 evaluable)	5 people were lost to long-term follow-up: 2 explanted due to intolerance of paraesthesia; 3 explanted due to delayed infection (1 person was subsequently re-implanted)	

Study	Participants	Adverse events	Comments
		CH attacks recurred in all people who were pain free at middle follow-up. 4 people relapsed into episodic attacks; 6 relapsed into chronic. 2/10 people experienced lead migration (surgery required) 5/10 people discontinued due to sustained improvement without stimulation.	
AE: adverse events; CH: cluster headaches; IPG: implantation of a permanent generator.			

7. Economic evaluation

7.1. Cost effectiveness

No studies evaluating the cost-effectiveness of occipital nerve stimulation were identified. Two studies were identified that estimated costs or cost savings associated with the use of occipital nerve stimulation. However, the studies were non-comparative and therefore did not meet the inclusion criteria for this evidence review. The studies are briefly described below.

Mueller et al. (2013) evaluated overall direct treatment costs for bilateral occipital nerve stimulation for 27 people within a 47 month period in a single centre in Germany. This included overall hospitalisation costs of €255,024 (£259,024[1]) and occipital nerve stimulation hardware costs of €516,019 (£524,113[1]), resulting in a total cost of €761,043 (£783,1371[1]), or €28,186 (£29,005[1]) per person over the study period. The study observed a reduction in triptan (before and after occipital nerve stimulation was used) that translated to a saving of €5,851 (£5,943[1]) per person per year. The authors concluded that occipital nerve stimulation had a relatively high initial cost but that total costs may decrease over time due to individual treatment costs.

Miller et al. (2017) estimated potential cost savings through triptan reduction following occipital nerve stimulation from the perspective of the UK NHS. The cost for triptan use was estimated to be over £9,000 per person per year. Based on a significant reduction in triptan use before and after occipital nerve stimulation, there was estimated to be a cost saving of £4,886 per person per year. When classifying participants as responders (more than 50% improvement in attack frequency) or non-responders, the annual cost saving was £7,252 and £2,224 per person, respectively.

7.2. Exploratory cost-utility analysis

An exploratory cost-utility analysis was undertaken to estimate the cost-utility of occipital nerve stimulation in comparison to standard care. The analysis took a NHS and Personal Social Services (PSS) perspective. Outcomes were estimated over a lifetime horizon and costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

The cost associated with occipital nerve stimulation (including equipment costs as well as hospital costs for the procedure) was based on the estimate of £29,005[2] from Mueller et al. (2013). The potential cost savings that may be accrued through a reduction in triptan use were based on resource use estimates from Miller et al. (2017), which was preferred over the estimates from Mueller et al. (2013) because it reflects the UK NHS perspective. (Miller et al. 2017) reported that the mean number of triptan doses per month was 36.8 before occipital nerve stimulation and 19.5 after occipital nerve stimulation. The cost per dose of triptan was estimated to be £23.43 based on an average of prices for sumatriptan 6 mg subcutaneous injection from the British National Formulary (Joint Formulary Committee 2019). The resulting cost of triptan use per year was therefore estimated to be £10,351 per year in people before occipital nerve stimulation and £5,485 following occipital nerve stimulation use. However, it is unclear whether the reduction in triptan use following occipital nerve stimulation would be sustained over time and as such the length of time that the saving was applied was varied (see subsequent section on modelled scenarios).

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[1] Values from Mueller 2013 converted and inflated to 2018 UK prices using the CCEMG-EPPI-Centre cost converter; Version 1.6. The Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre).

[2] Original value converted and inflated to UK 2018 prices using the CCEMG-EPPI-Centre cost converter

Quality-adjusted life-years (QALYs) were estimated under the assumption that survival rates in people with chronic cluster headaches would be the same as those of the general population. Furthermore, since no differences in survival were identified in our evidence review, it was assumed that mortality rates would be equivalent in people using occipital nerve stimulation or standard care. Mortality rates were estimated using life tables from the Office for National Statistics (ONS 2019), which reports mortality probabilities based on age and gender. Mortality rates were estimated assuming that 65% of the population were male and that the average age was 48 years old. These values were estimated by taking a weighted average of age and gender from the studies identified in our evidence review.

The mortality estimates were used to estimate patient life years over their expected lifetime. These life year estimates were then combined with quality-of-life estimates to generate QALYs. EQ-5D data from Fontaine et al. (2017) and Miller et al. (2017) were used to estimate quality of life as EQ-5D is the preferred measure in health economic analyses. The results of Fontaine et al. (2017) and Miller et al. (2017) are divergent as one study shows a difference in quality of life before and after occipital nerve stimulation (increased from 0.38 to 0.55 in Fontaine et al. [2017]) while the other does not (0.69 before and after occipital nerve stimulation in Miller et al. [2017]). The reason for this difference is unclear but it may be a result of the different follow-up times of each study (12 months in Fontaine et al. [2017] and 39 months in Miller et al. [2017]), perhaps suggesting that the initial quality of life gain diminishes over time.

To reflect the uncertainty around the quality of life effect as well as uncertainty around the reduction in triptan use, various scenarios were modelled, in which these two aspects were varied. Table 5 lists the six scenarios that were modelled.

Table 5: Modelled scenarios

Quality-of-life assumption	Triptan use assumption	
	Reduction in triptan use only applied in first year	Reduction in triptan use applied over modelled time horizon
Quality of life values from Fontaine 2017 applied in initial year but observed difference diminishes over time and values are equivalent at three years.	Scenario 1a	Scenario 1b
Quality of life values from Fontaine 2017 were applied and maintained over the modelled time horizon.	Scenario 2a	Scenario 3b
Quality of life values from Miller 2017 were applied and maintained over the modelled time horizon (i.e. no difference in quality of life).	Scenario 3a	Scenario 3b

The results of the exploratory analysis are shown in Table 6. The table lists the overall costs and QALYs for each of the strategies over the modelled time horizon. The resulting incremental cost effectiveness ratio (ICER), i.e. cost per QALY gained, was used to determine whether occipital nerve stimulation would be deemed cost-effective. ICER values below the commonly applied threshold of £20,000 per QALY gained were considered cost effective.

It can be seen that the results differ greatly depending upon the assumptions that are made around quality of life and triptan use over time. In comparison to standard care, occipital nerve stimulation was found to be equally effective or more effective while also cost saving (i.e.

dominant) in all scenarios where it was assumed that the reduction in triptan use was maintained over time. When it was assumed that the triptan use reduction only applied in the first year, occipital nerve stimulation was found to be more costly in all scenarios. The cost effectiveness of occipital nerve stimulation in these scenarios was dependent upon the assumption made around quality of life. In the scenario where quality of life returns to baseline at three years, occipital nerve stimulation was found to be more effective than standard care but not cost-effective as the resulting ICER (£100,142 per QALY gained) was above the threshold of £20,000 per QALY gained. In the scenario where the quality of life benefit was assumed to be maintained over time, occipital nerve stimulation was found to be more effective than standard care and cost effective as the resulting ICER (£7,556 per QALY gained) was below the threshold of £20,000 per QALY gained. In the scenario where no difference in quality of life was assumed, occipital nerve stimulation was found to be as effective as standard care but more costly and was therefore considered to be dominated.

Table 6: Results of exploratory cost-utility analysis

Treatment strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Scenario 1a (QoL returns to baseline at three years, triptan use reduction in first year only)					
Standard care	£195,932	-	7.19	-	-
Occipital nerve stimulation	£220,247	£24,315	7.44	0.24	**£100,142**
Scenario 1b (QoL returns to baseline at three years, triptan use reduction in all years)					
Standard care	£195,932	-	7.19	-	-
Occipital nerve stimulation	£132,825	−£63,108	7.44	0.24	**Dominant**
Scenario 2a (QoL benefit maintained in all years, triptan use reduction in first year only)					
Standard care	£195,932	-	7.19	-	-
Occipital nerve stimulation	£220,247	£24,315	10.41	3.22	**£7,556**
Scenario 2b (QoL benefit maintained in all years, triptan use reduction in all years)					
Standard care	£195,932	-	7.19	-	-
Occipital nerve stimulation	£132,825	−£63,108	10.41	3.22	**Dominant**
Scenario 3a (no difference in QoL, triptan use reduction in first year only)					
Standard care	£195,932	-	13.06	-	-
Occipital nerve stimulation	£220,247	£24,315	13.06	0.00	**Dominated**
Scenario 3b (no difference in QoL, triptan use reduction in all years)					
Standard care	£195,932	-	13.06	-	-

Treatment strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Occipital nerve stimulation	£132,825	−£63,108	13.06	0.00	**Dominant**
QoL, quality of life; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio					

7.3. Resource impact analysis

The population that may receive occipital nerve stimulation was estimated based on a cluster headache prevalence of 69 in 100,000 people in the UK (Fuller&Kaye 2007). Applying this prevalence rate to the estimated population of Wales (3,138,631) from the Office for National Statistics in 2018 gives an estimated 2,166 people with cluster headaches in Wales. Around 15-20% of cluster headaches were estimated to be chronic (Láinez&Guillamón 2017) and between 5% and 20% of people with chronic cluster headaches were estimated to develop drug-resistant headaches (Láinez&Guillamón 2017, Leone et al. 2017, Mueller et al. 2013). Applying the midpoint of these rates to the estimated population with cluster headaches in Wales (2,166) results in an estimated 47 people with medically refractory chronic cluster headaches in Wales.

The unit costs specified in the cost-utility analysis section above were used in the budget impact analysis. Thus, a cost of £29,005 was applied for occipital nerve stimulation (based on equipment and hospitalisation costs from Mueller et al. [2013]) and £23.43 was used for the cost per dose of triptan. Two scenarios were modelled reflecting the uncertainty around whether the reduction in triptan use would be sustained over time. In one scenario, the reduction was applied in the first year only whereas in the other it was assumed to apply over the modelled time horizon of five years. Table 7 gives the estimated resource impact of introducing occipital nerve stimulation in the scenario where the triptan reduction was applied in the first year only.

Table 8 gives the estimated resource impact of introducing occipital nerve stimulation in the scenario where the triptan reduction was over the modelled time horizon of five years.

It can be seen that the initial cost of introducing occipital nerve stimulation in people with medically refractory chronic cluster headaches in Wales was estimated to be £1,374,078. In the scenario where the triptan reduction was only applied in the first year (Table 7), the initial cost outweighs the savings of £468,712 associated with a reduction in triptan use and the resulting cost impact was estimated to be £905,366. In the scenario where the triptan reduction was applied in all five years (

Table ***8***), the initial cost is offset by the savings of £1,390,842 associated with a reduction in triptan use, resulting in overall cost savings of £16,764.

Table 7: Resource impact analysis in scenario where triptan reduction was applied in first year only

Cost items	Cost for estimated population with medically refractory chronic cluster headaches in Wales (n=47)		
	Standard care	Occipital nerve stimulation	Impact
Occipital nerve stimulation cost for population (equipment and hospitalisation)	-	£1,374,078	£1,374,078
Triptan costs in year one	£490,365	£21,653	−£468,712
Triptan costs in years two to five	£1,961,458	£1,961,458	£0
Total costs	**£2,451,823**	**£3,357,189**	**£905,366**

Table 8: Resource impact analysis in scenario where triptan reduction applied in all five years

Cost items	Cost for estimated population with medically refractory chronic cluster headaches in Wales (n=47)		
	Standard care	Occipital nerve stimulation	Impact
Occipital nerve stimulation cost for population (equipment and hospitalisation)	-	£1,374,078	£1,374,078
Triptan costs in year one to five	£2,451,823	£1,060,981	−£1,390,842
Total costs	**£2,451,823**	**£1,060,981**	**−£16,764**

8. Organisational issues

Occipital nerve stimulation for medically-refractory chronic cluster headache is not provided through NHS Wales, but it is commissioned through NHS England (NHS England 2015). Access for eligible Welsh patients is through individual patient funding requests and referral to NHS England; currently less than five people are referred each year through this process.

Expert opinion advises that, should occipital nerve stimulation be made available, delivering the service in Wales would be beneficial as the treatment requires regular follow-ups for stimulation programming, device maintenance and optimising oral medications. However, the main barrier to deliver this care in Wales is the lack of cluster headache multi-disciplinary teams or specific expertise for occipital nerve stimulation in Wales. Therefore, delivery of occipital nerve stimulation in Wales would require adequate training and the development of specialist teams or centres. The NHS England commissioning policy notes that adverse event profile for occipital nerve stimulation has improved due to increasing surgical experience and improved surgical techniques (NHS England 2015). This may be restricted by the number of people that would be eligible for occipital nerve stimulation, due to the small population size.

The NHS England commissioning policy also recommends that clinicians should report details for all patients undergoing occipital nerve stimulation for chronic migraine or chronic cluster headache should be included onto the UK Neuromodulation Register.

9. Patient issues

Chronic cluster headaches is a severe, disabling condition, and people with medically refractory headaches have limited options for treatment. Therefore, offering occipital nerve stimulation would provide an additional option for patients where current options have failed. Expert comment noted that if occipital nerve stimulation was routinely available, providing it closer to home, in Wales, would be better as long journeys are difficult for people with chronic cluster headaches.

Our searches identified quality of life data from two studies, which demonstrated that chronic cluster headache is severely debilitating for people with the condition. In Magis et al. (2016), the self-reported PGIC score showed 55.4% of patients felt that their condition was improved or very improved after occipital nerve stimulation. One of the studies identified in this review reported that 60% (6/10) of patients were satisfied with treatment (Magis et al. 2016); the main reason for dissatisfaction was the need for repeated surgery.

We also identified two additional patient studies. The first study explored acute and preventative treatment preferences for people with headaches (Mitsikostas et al. 2017). The study included 514 participants in total. Compared to people with episodic headaches, people with chronic headaches reported that they would prefer neurostimulation over daily pharmaceutical treatment (odds ratio = 1.5; 95% confidence interval 1.1 to 2.1; p = 0.013). Twenty-one participants in the study had chronic cluster headaches; the majority viewed efficacy as more important than safety or route of administration for both symptomatic and preventative treatment.

The second paper was a conference paper reporting patient satisfaction for rechargeable systems in occipital nerve stimulation for cluster headache (Sciacca et al. 2013). Patients (n = 92) were identified through a London centre and given questionnaires. The majority (74%) found recharging the battery convenient, while 88% found that the amount of inconvenience was outweighed by the benefit received from stimulation. 53% of patients had experienced occipital nerve stimulation with a non-rechargeable battery, 84% of which reported a preference for the rechargeable version.

10. Conclusions

This review identified evidence for occipital nerve stimulation to treat medically refractory chronic cluster headaches. The manufacturer of the electrodes, leads and batteries, as well as the application of unilateral or bilateral electrodes, varied across the studies.

Overall, the published evidence showed that occipital nerve stimulation has the potential to improve the condition and patient quality of life, particularly in terms of attack frequency. However, the current evidence is limited to several case series, ranging between eight and 51 participants. The patient numbers, outcomes and analysis vary across the studies. Lack of randomisation, lack of blinding and lack of control can all lead to a high risk of bias. It is worth noting that small participant numbers may be partly due to the rarity of the condition (people with chronic cluster headaches that are resistant to drugs).

Adverse events reported in clinical studies are common and include hardware issues (battery failure, lead migration) and biological issues (infections). Complications often required surgical intervention. Surgical intervention is also required for expected battery replacement.

Evidence from cost studies shows that the initial cost of occipital nerve stimulation is high but that this cost may be offset, at least partially, by a reduction in medication costs (particularly triptan use). An exploratory cost-utility analysis conducted for this report demonstrated that the duration of the treatment effect, in terms of its effect on triptan use and quality of life, was a key aspect in determining whether occipital nerve stimulation would be cost-effective. Similarly, the resource impact analysis demonstrates that the use of occipital nerve stimulation has the potential to be cost saving if there is a prolonged reduction in the use of triptans. Conversely, there could be a substantial cost increase if the reduction in triptan use only applies in the short-term.

11. Further research

More evidence generated through randomised control trials using sham control is warranted. It is acknowledged that use of placebo or blinding could prove difficult due to the necessary induction of paraesthesia in trial participants. However, it is noted that this may be possible due to the increased usage of high-frequency stimulation that does not induce paraesthesia, or through burst frequency stimulation techniques.

A national registry for implantable devices (occipital nerve stimulation and others) in all headache conditions would be beneficial to establish long-term monitoring of these devices, including their safety and efficacy.

12. Contributors

This topic was proposed by Andrew Champion, Welsh Health Specialised Services Committee.

The HTW staff and contract researchers involved in writing this report were:

- J Washington – literature search
- L Elston – clinical and lead author
- M Prettyjohns – health economics author and report editor
- D Jarrom – editor
- A Mironas – clinical quality assurance check
- S Hughes – health economics quality assurance check
- H Britton – project management

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of HTW.

Experts who contributed to this appraisal:

- N Silver – Consultant Neurosurgeon and clinical lead for headache, Liverpool
- C Patel – Consultant Neurosurgeon, Cardiff and Vale
- One expert who provided patient perspective.

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Appendix 1. PICO framework

Research Question	Is occipital nerve stimulation clinically and cost effective in patients with medically refractory chronic cluster headaches?

	Inclusion criteria	Exclusion criteria
Population	Adults with medically refractory chronic cluster headaches	Patients with chronic migraines
Intervention	Occipital nerve stimulation	
Comparison/ Comparators	Best alternative care – SHAM therapy	
Outcome measures	• Patients improved >50% • Change in attack frequency (%) • Change in attack severity (%) • Preventative treatment reduction • Quality of Life • Adverse events	
Study design	Systematic reviews or primary studies assessing the effectiveness of occipital nerve stimulation, which could include: • randomised trials, • prospective or retrospective longitudinal cohort studies • cross-sectional studies We will only include evidence for "lower priority" evidence where outcomes are not reported by a "higher priority" source (systematic review or randomised study). We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison	

Appendix 2. PRISMA diagram