NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine

Cluster headaches are attacks of severe pain on one side of the head, usually around the eye. Other symptoms include a red and watery eye and a runny nose. They can happen several times a day and last from minutes to hours. Migraines are severe headaches, usually felt as a throbbing pain at the front or side of the head, which can be accompanied by nausea and sensitivity to light. They may last for several hours. In this procedure, the patient uses a small handheld device to stimulate nerves on the side of their neck with the aim of relieving pain and reducing the number of headache attacks.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) 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 IP overview was prepared in August 2015.

Procedure name

- Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine

Specialist societies

- Association of British Neurologists
- Neuromodulation Society of UK and Ireland
- British Association for the Study of Headache

Description

Indications and current treatment

Cluster headaches are characterised by episodes of unilateral periorbital pain, conjunctival injection, lacrimation and rhinorrhoea. Attacks can last from a few minutes to several hours and can occur many times a day, over several days. Migraines are severe headaches, often accompanied by nausea, photophobia and phonophobia. In some people, migraines may be accompanied by aura which is characterised by the perception of flashing lights, the perception of unpleasant odours, confusion or difficulty speaking.

The usual treatment option for patients with cluster headache or migraine is medical therapy, either to prevent or stop acute attacks. Medical treatments for acute cluster headache attacks include oxygen inhalation and medications such as triptans. Corticosteroids and verapamil may be used to prevent or reduce the frequency of cluster headaches. Medical treatments for acute migraine attacks include analgesics, triptans and anti-emetics. Beta-blockers, tricyclic antibiotics, pizotifen and anticonvulsants may be used to prevent or reduce the frequency of migraine attacks.

Surgical treatments are reserved for patients with distressing symptoms that are refractory to medical treatments. For patients with chronic cluster headache, surgical treatments include deep brain stimulation to modulate central processing of pain signals, and radiofrequency ablation to interrupt trigeminal sensory or autonomic pathways. For patients with chronic migraine, surgical treatments include occipital nerve blocks and occipital nerve stimulation.

What the procedure involves

Transcutaneous vagus nerve stimulation uses low voltage electrical currents to stimulate the cervical branch of the vagus nerve. The aim is to relieve pain and reduce the frequency of attacks for both cluster headaches and migraine.

Therapy is self-administered by the patient, using a handheld device the size of a mobile phone. The patient places the device on the side of the neck, over the cervical branch of the vagus nerve, positioning its 2 smooth metal stimulation

surfaces in front of the sternocleidomastoid muscle, over the carotid artery. The patient slowly increases the stimulation strength until small muscle contractions are felt under the skin; stimulation is then applied for approximately 90 seconds. The device can be used to treat acute attacks, and as prophylaxis between attacks.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine. The following databases were searched, covering the period from their start to 11 August 2015: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with cluster headache and migraine.
Intervention/test	Transcutaneous stimulation of the cervical branch of the vagus nerve.
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 IP overview

This IP overview is based on 214 patients from 1 randomised controlled trial and 4 case series.

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 2a Summary of key efficacy and safety findings on transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine

Study 1 Gaul C– Treatment of cluster headache

Details

Study type	**Randomised controlled trial**
Country	Multicentre: Germany, United Kingdom, Belgium, and Italy
Recruitment period	2012 to 2014
Study population and number	Patients with chronic cluster headache **n=97 (48 treated by standard care plus transcutaneous vagus nerve stimulation [tVNS] versus 49 treated by standard prophylactic medication)**
Age and sex	Standard care plus tVNS group: mean age, 45.4 years; 71% (34/48) male Standard care alone group: mean age, 42.3 years; 67% (33/49) male
Patient selection criteria	Inclusion criteria: patients aged between 18 and 70 years with chronic cluster headache, according to International Classification of Headache Disorders criteria, were included. Exclusion criteria: patients with a history of intracranial/carotid aneurysm or haemorrhage, brain tumours, significant head trauma, cardiovascular disease, previous carotid endarectomy, previous vascular neck surgery or abnormal anatomy at the tVNS treatment site were excluded. Patients who were implanted with electrical or neurostimulation devices or those who had changed the prophylactic medication type or dosage within a month of enrolment were also excluded.
Technique	Patients were randomised to receive a 4-week course of standard care plus tVNS or standard care alone **(randomisation phase)**. In the tVNS group, were asked to prophylactically treat attacks by applying 3×2 minute doses of stimulation to the right side of the neck, at 5 minute intervals, 2 times a day. The first prophylactic treatment was administered within 1 hour of waking; the second treatment was administered 7 to 10 hours after the first treatment. Patients also had the option of acutely treating cluster headache attacks with 3 doses of tVNS on pain onset. Patients were instructed to take rescue medications if the attack did not stop within 15 minutes after neurostimulation. At the end of the 4-week randomisation phase, patients in both groups were given the option of receiving tVNS for an additional 4 weeks **(extension phase)**.
Follow-up	**Up to 8 weeks**
Conflict of interest/source of funding	The study was funded by the manufacturer.

Analysis

Follow-up issues: 92 patients (44 standard care plus tVNS versus 48 standard care-alone) continued into the extension phase and 70 patients (33 standard care plus tVNS versus 37 standard care-alone) completed the study.

Study design issues: Authors stated that 'a sample size of 40 subjects per treatment arm had 80% power to detect between-group differences in mean change from baseline using a 2-sided test with $\alpha \leq 0.05$'. The intention-to-treat population was defined as all patients who had ≥1 efficacy reading after randomisation (n=93; 45 standard care plus tVNS versus 48 standard care-alone). The modified intention-to-treat population was defined as patients who had measurable observations across respective study phases: numbers varied according to each outcome measure.

Study population issues: Use of standard prophylactic medications was similar between groups. The percentages of patients who were >80% adherent to their treatment regimens during the randomised and extension phases of the study were 64.4% in the standard care plus tVNS group and 50% in the standard care group.

Other issues: A response was defined as greater than a 50% reduction in the mean number of cluster headache attacks per week. The response rate was assessed during the last 2 weeks of the randomisation and extension (additional 4 weeks of tVNS) phases of the study.

- Pain intensity was evaluated using a 5-point scale (1 to 5) with lower scores indicating less pain.
- EQ-5D scores range from 0 to 100 with higher scores indicating better quality of life.
- Headache impact test (HIT)-6: scores range from 36 to 78 with lower scores indicating better quality of life.
- Patient satisfaction was measured using a 5-point scale (1 to 5) with lower scores indicating greater satisfaction.
- Ease of device use was measured using a 4-point scale (1 to 4) with a score of 1 indicating that the device was very easy to use and a score of 4 indicating that the device was very hard to use.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **93 patients (45 standard care plus tVNS versus 48 standard care-alone); however, numbers varied according to outcome measure.**

Attack frequency

- The mean number of cluster headache attacks per week decreased by 5.9 attacks in the standard care plus tVNS group (n=45) and 2.1 attacks in the standard care alone group during the randomisation phase (n=48; p value between groups=0.02). Baseline measurements were not reported.
- During the extension phase the mean number of cluster headache attacks per week decreased from 9.6 to 7.6 in patients who were initially in the standard care plus tVNS group (n=30; p<0.001) and from 15.7 to 12.4 in patients who were initially in the standard care alone group (n=41; p<0.001).

Response rates in the intention-to-treat population (45 standard care plus tVNS versus 48 standard care-alone): a response was defined as >50% reduction in attack frequency

- The response rate was 40% (18/45) in the standard care plus tVNS group and 8% (4/48) in the standard care alone group during the randomisation phase (p<0.001). During the extension phase the response rate was 28.9% (13/45) in patients who were initially in the standard care plus tVNS group and 16.7% (8/48) in patients who were initially in the standard care alone group (p<0.001).

Use of rescue medication in the <u>modified</u> intention-to-treat population

- The mean number of times subcutaneous sumatriptan was used decreased from 7.2 to 2.8 in the standard care plus tVNS group (n=32; p=0.007) and increased from 6.8 to 7.5 in the standard care alone group (n=42; not significant) during the last 2 weeks of the randomisation phase. During the last 2 weeks of the extension phase, the mean number of times subcutaneous sumatriptan was used increased from 2.4 to 4 in the standard care plus tVNS group (n=27) and from 7.1 to 7.5 in the standard care alone group (n=32). No p values reported.
- The mean number of times inhaled oxygen was used decreased from 17.3 to 6.5 in the standard care plus tVNS group (n=32; p=0.02) and from 12.6 to 10.8 in the standard care alone group (n=42; not significant) during the last 2 weeks of the randomisation phase. During the last 2 weeks of the extension phase, the mean number of times inhaled oxygen was used increased from 7.0 to 8.0 in the standard care plus tVNS group (n=27) and decreased from 12.4 to 10.1 in the standard care group (n=32). No p values reported.

Quality of life: changes from baseline

	Mean change from baseline to end of randomisation phase			Mean change from baseline to end of extension phase		
Outcome measure	Standard care plus tVNS group	Standard care alone	p value	Standard care plus tVNS group	Standard care alone	p value
EQ-5D	9.20	0.27	0.039	10.79	4.36	NR
HIT-6	-2.78	-0.47	NR	-3.28	-2.77	NR

NB: baseline scores were not reported

Patient satisfaction

- At the end of the study, 65% (62/96) of patients stated that they would recommend tVNS to others and over 75% (72/96) of patients rated the device as easy to use.

Safety

	Percentage (n/N)	
Adverse event	Standard care plus tVNS group	Standard care-alone
Induced cluster headache attack	2 (1/48)	10 (5/49)
Dizziness	6 (3/48)	6 (3/49)
Headache	8 (4/48)	2 (1/49)
Nasopharyngitis	2 (1/48)	8 (4/49)
Oropharyngeal pain	6 (3/48)	2 (1/49)
Neck pain	6 (3/48)	0

- Authors stated that 1 or more of the following device-related adverse events were reported in 27% (13/48) of patients in the standard care plus tVNS group: depressed mood, malaise, oropharyngeal pain, induced cluster headache, muscle twitching, muscle spasms, hot flushes, acne, pain, throat tightness, dizziness, hyperhidrosis, toothache, decreased appetite and skin irritation.
- Authors stated that 1 or more of the following device-related adverse events were reported in 14% (7/49) of patients in the standard care group: erythema, facial oedema, induced cluster headache, chest pain, fatigue, depressed mood, pruritus, musculoskeletal stiffness and parosmia. All occurred during the extension phase of the study.

Abbreviations used: HIT, headache impact test; NR, not reported; tVNS, transcutaneous vagus nerve stimulation

Study 2 Nesbitt AD (2015) – Treatment of cluster headache

Details

Study type	**Case series**
Country	United Kingdom
Recruitment period	2012
Study population and number	Patients with episodic and chronic cluster headache **n=19**
Age and sex	Median age, 49 years; 58% (11/19) male
Patient selection criteria	Inclusion criteria: patients with episodic (a series of cluster headache bouts, each one lasting more than a week and separated by pain-free remission lasting more than two weeks) or chronic cluster headache (no pain-free remission) were included. Exclusion criteria: patients implanted with active neurostimulation devices or cardiac pacemakers, or patients who had a significant history of autonomic disorders or cardiac arrhythmia were excluded.
Technique	Patients treated each acute attack with up to 3×120 second doses of electrical stimulation. For prevention, patients administered 2 doses of stimulation in the morning and 2 doses in the afternoon (approximately 8 hours apart).
Follow-up	**1 year**
Conflict of interest/source of funding	The study received unrestricted funding from the manufacturer.

Analysis

Follow-up issues: One patient discontinued tVNS after a tapering course dose of corticosteroids. It is unclear how long they were using the neurostimulator device.

Study design issues: Patients were recruited from 2 headache centres. Vagus nerve stimulation was given as adjunct or first-line treatment. Patients received training on appropriate use of the neurostimulator device.

Study population issues: A history of chronic cluster headache was reported in 58% (11/19) of patients; the remaining patients had episodic cluster headache. Drug-refractory cluster headache was reported in 37% (7/19) of patients. A history of concurrent migraine (with or without aura) was reported in 58% (11/19) of patients. One patient had previously been implanted with an occipital nerve stimulator but their headaches became unresponsive to neurostimulation 2 years after implantation. The patient chose to have the pulse generator removed but the leads were left in situ. Four patients had changes in their headache medication during the follow-up period. Two of these patients had preventative medication withdrawn; 1 commenced methysergide as a substitute and the other had a pre-existing dose of verapamil increased. Of the other 2 patients who had changes in their headache medication, 1 was prescribed high-flow oxygen and the other commenced a tapering dose of corticosteroids.

Other issues: Outcome measures were based on patients' estimates of benefit. Patients were asked, with the aid of their headache diaries, to provide percentage estimates of their perceived overall change in condition, the percentage change in acute medication use, the percentage of attacks they were able to treat acutely and the proportion of attacks that they were able to terminate (complete resolution of pain) within 15 minutes of neurostimulation.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **19 patients** **Improvements in symptoms** • An improvement in symptoms was reported in 79% of patients at 1-year follow-up. The mean percentage improvement in headache pain was 48%. **Acute treatment** • Complete resolution of pain was achieved in 47% of cluster headache attacks within a mean of 11±1 minutes of starting neurostimulation. **Headache prevention** • The mean number of cluster headache attacks per day decreased from 4.5 to 2.6 at 1-year follow-up ($p<0.0005$). **Changes in rescue medication use** • A reduction in the use of oxygen inhalation was reported in 75% (12/16) of patients. Of these patients, 2 patients who were using oxygen inhalation as their only acute treatment, stopped using the treatment and preferred to use the tVNS device as their only acute treatment. • A 100% increase in the use of oxygen inhalation was reported in 1 patient. • A reduction in the use of triptans was reported in all patients who used triptans: 4 stopped treatment altogether (3 of which continued to used oxygen inhalation) and 9 reduced their triptan use by a mean of 48±6%. • No patients reported an increase in the use of triptans during the follow-up period.	• Adverse events included local discomfort, during or after neurostimulation; however authors did not report incidence rates. • Transient worsening of headache was reported in 1 patient. • Shifting of the side of headaches was reported in 2 patients.
Abbreviations used: tVNS, transcutaneous vagus nerve stimulation	

Study 3 Barbanti P (2015) – Treatment of migraine

Details

Study type	**Case series**
Country	Italy
Recruitment period	2013
Study population and number	Patients with high-frequency episodic or chronic migraine **n=50**
Age and sex	Mean age, 43.2 years; 20% (10/50) male
Patient selection criteria	Inclusion criteria: patients aged between 18 and 65 years with high-frequency episodic migraine (more than 8 headache days per month with or without aura) or chronic migraine (more than 15 headache days per month) were included. Exclusion criteria: patients with a history of cerebrovascular, cardiovascular, atherosclerotic or significant neurological disease were excluded. Patients who were implanted with an electronic device were also excluded.
Technique	Patients were asked to treat a maximum of 3 consecutive migraine attacks within a 2 week evaluation period. For each migraine attack, patients delivered 2×120 second doses of stimulation to the right cervical branch of the vagus nerve at 3 minute intervals. They were instructed to start neurostimulation within 20 minutes of migraine/pain onset. They were allowed to take rescue medication if they perceived no reduction in pain 2 hours after neurostimulation.
Follow-up	**2 weeks**
Conflict of interest/source of funding	One author was an employee of the manufacturer while another author acted as a scientific adviser to the manufacturer.

Analysis

Follow-up issues: Two patients did not treat any migraine attacks

Study design issues: Authors state that multiple centres; however, the number of participating centres was not reported. Patients received training on the proper use of the stimulation device from a physician as well as an instructional video.

Study population issues: 28% (14/50) of patients had high-frequency episodic migraine whereas 72% (36/50) of patients had chronic migraine. The proportion of patients with a history of allodynia was 36% (18/50). Medication overuse headache was reported in 10% (5/50) of study participants; all of whom had chronic migraine. The majority of patients treated more than 1 migraine attack during the 2-week evaluation period: 36 patients treated 3 attacks, 11 patients treated 2 attacks, and 1 patient treated 1 attack. Authors did not state which attacks were accompanied by nausea, photophobia or photophobia at baseline.

Other issues: Pain severity was measured at baseline (migraine onset), 1 hour after neurostimulation and 2 hours after neurostimulation using a visual analogue scale (VAS): scores ranged from 0 to 10 with lower scores indicating less pain. **Pain relief was defined as greater than a 50% reduction in VAS scores.** Complete resolution of pain was defined as a VAS score of 0.

- Patient satisfaction was assessed using a Likert scale: scores ranged from 1 to 5 with higher scores indicating greater satisfaction.

- Authors do not state how functional disability was measured.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **48 patients (131 attacks)**

Pain relief and complete resolution of pain (proportion of treatments)

	1 hour after neurostimulation		2 hours after neurostimulation	
	Proportion that resulted in pain relief (%) [n/N]	Proportion that resulted complete resolution of pain (%) [n/N]	Proportion that resulted in pain relief (%) [n/N]	Proportion that resulted complete resolution of pain (%) [n/N]
All attacks	38 [50/131]	18 [23/131]	51 [67/131]	23 [30/131]
HFEM	46 [15/33]	30 [10/33]	61 [20/33]	33 [11/33]
CM	36 [35/98]	13 [13/98]	48 [47/98]	19 [19/98]

- The proportion of patients who had pain relief in over 50% of attacks at 2 hours after neurostimulation was 62.5% (78.6% in the high-frequency episodic migraine group and 55.9 % in chronic migraine group). Numerators and denominators were not reported.
- The proportion of patients who had pain relief in over 50% of attacks at 2 hours after neurostimulation was 33.3% (50% in the high-frequency episodic migraine group and 26.5% in chronic migraine group). Numerators and denominators were not reported.
- Authors stated that achievement of pain-free status at 1 and 2 h for at least 1 attack was experienced in 33.3% (11/33) of patients who treated 3 attacks and 41.7% (5/12) of patients treating who treated 2 attacks (5/12).

Improvements in associated symptoms at 2 hours

	Proportion of treatments (%) [n/N]
Relief of nausea	66 [87/131]
Relief of photophobia	76 [100/131]
Relief of phonophobia	77 [101/131]

NB: authors did not report the number of attacks which were accompanied by each of the associated symptoms above

- Complete recovery from functional disability was reported in 35% (46/131) of patients.

Need for rescue medication

- Rescue medication was needed in 53% (70/131) attacks 2 hours after neurostimulation.

Patient satisfaction

- A satisfaction score of 4 or 5 (satisfied or very satisfied) was reported in 46% (22/48) of patients.

Safety

- Mild tingling was reported in 67% (32/48) of patients.

Abbreviations used: HFEM, high-frequency episodic migraine; CM, chronic migraine

Study 4 Goadsby PJ (2015) – Treatment of migraine

Details

Study type	**Case series**
Country	United States
Recruitment period	2012
Study population and number	Patients with migraine (with or without aura) **n=30**
Age and sex	Median age, 39 years; 17% (5/30) male
Patient selection criteria	Inclusion criteria: patients aged between 18 and 55 years diagnosed with migraine (with or without aura), according to International Classification of Headache Disorders second edition criteria, who had at least 2 migraines per month and less than 15 headache days per month during the preceding 3 months were included. The age of onset of migraines was less than 50 years in all participants. Exclusion criteria: patients with a history or documentation of seizure, syncope, aneurysm, intracerebral haemorrhage, brain tumours, significant head trauma, atherosclerotic cardiovascular disease, severe carotid artery disease, congestive heart failure, unstable cardiac arrhythmia second degree heart block type II, ventricular tachycardia, ventricular fibrillation, previous bilateral or right cervical vagotomy, uncontrolled hypertension, previous carotid endarterectomy or vascular neck surgery were excluded. Patients who were implanted with an electrical and/or neurostimulator device, who took medication for acute headaches for more than 10 days per month or who failed to respond to more than two classes of treatment for episodic migraine were excluded.
Technique	Patients were asked to treat up to 4 acute migraine attacks with the device within 4 weeks. Each treatment consisted of 2×90 second doses of stimulation at 15 minute intervals, delivered to the right cervical branch of the vagus nerve. Patients were asked to self-treat once pain became moderate or severe, or after 20 minutes of mild pain. They were allowed to take rescue medication if they perceived no reduction in pain 2 hours after neurostimulation.
Follow-up	**6 weeks**
Conflict of interest/source of funding	The study was sponsored by the manufacturer.

Analysis

Follow-up issues: Three patients were unable to provide efficacy data; 2 patients did not use the device to treat any attacks while 1 patient only used the device to treat aura.

Study design issues: The study was conducted at 4 headache centres which advertised for patients (self-selecting) or enrolling patients already attending the clinic. Thirteen patients treated 4 attacks, 5 patients treated 3 attacks, 4 patients treated 2 attacks and 5 patients had 1 attack each. Initial analysis of efficacy was based on each patient's first attack alone. Subsequently, authors assessed all migraine attacks.

Study population issues: A history of migraine with aura was reported in 40% (10/30) of patients.

Other issues: Migraine pain was categorised as none, mild, moderate or severe. **Pain relief was categorised as moderate to severe pain at baseline that reduced to mild or no pain 2 hours after stimulation.**

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **27 patients (80 attacks)** **Acute treatment of pain during an initial migraine attack** • Pain relief at 2 hours after neurostimulation was reported in 47% (9/19) of patients who had moderate to severe attacks. • Complete resolution of pain at 2 hours after neurostimulation was reported in 21% (4/19) of patients who had moderate to severe attacks. • Complete resolution of pain at 2 hours after neurostimulation was reported in 5 out of 8 patients who had mild attacks. **Acute treatment of pain during all migraine attacks** • Pain relief was reported in 43% (23/54) of moderate to severe attacks 2 hours after neurostimulation. • Complete resolution of pain was reported in 22% (12/54) of moderate to severe attacks 2 hours after neurostimulation. • Complete resolution of pain was reported in 38% (10/26) of mild attacks 2 hours after neurostimulation. **Improvements in associated symptoms** • Relief of nausea was reported in 38% (11/29) of attacks which were accompanied by nausea. • Relief of photophobia was reported after 30% (16/53) of attacks which were accompanied by photophobia. • Relief of phonophobia was reported in 52% (17/33) of attacks which were accompanied by phonophobia.	Number of patients analysed: **28 patients** • A stiff neck was reported in 18% (5/28) of patients. • Mild lip or facial drooping was reported in 7% (2/28) of patients. • Frequent urination was reported in 14% (4/28) of patients. • Reddening of the skin around the treatment site was reported in 7% (2/28) of patients. • Moderate shoulder pain or spasm was reported in 7% (2/28) of patients. • Mild or moderate dizziness was reported in 7% (2/28) of patients. Symptoms lasted for up to 1 hour in 1 patient. • A single occurrence of each of the following was reported: coughing, sneezing, fatigue, a raspy voice, mild twitching of neck muscles, mild swelling of the neck, tinnitus in one ear, fever (39ºC), joint pain and mild confusion that lasted for 2 hours.

Study 5 Magis D (2013) – Treatment of various headache disorders

Details

Study type	**Case series – CONFERENCE ABSTRACT**
Country	Not reported
Recruitment period	Not reported
Study population and number	Patients with various primary headache disorders **n=18**
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: patients with migraine without aura (n=12), trigeminal autonomic cephalalgia (n=4) and hemicranias continua (n=2) were included. Exclusion criteria: not reported.
Technique	Patients were asked to prophylactically treat attacks by applying 90 seconds of tVNS, 3 times a day.
Follow-up	**Up to 8 weeks**
Conflict of interest/source of funding	Not reported
Safety outcomes	• Local discomfort was reported in 17% (3/18) of patients. • Tonic muscle contraction was reported in 17% (3/18) of patients. • Fatigue was reported in 1 patient. • Palpitations were reported in 1 patient. • Cervical muscle spasm was reported in 1 patient.

Efficacy of transcutaneous stimulation of the cervical branch of the vagus nerve for treating cluster headache

Attack frequency

In a randomised controlled trial of 97 patients with cluster headache treated by standard care plus transcutaneous vagus nerve stimulation (tVNS; n=48) or standard care alone (n=49), the mean number of cluster headache attacks per week decreased by 5.9 attacks in the standard care plus tVNS group and by 2.1 attacks in the standard care alone group at 4-week follow-up (p value between groups=0.02). Baseline measurements were not reported. During the extension phase of the study, patients from both groups received adjunctive tVNS for 4 additional weeks. In this period, the mean number of cluster headache attacks per week decreased from 9.6 to 7.6 in patients who were initially in the standard care plus tVNS group (n=30; p<0.001) and from 15.7 to 12.4 in patients initially in the standard care alone group (n=41; p<0.001)[1].

In a case series of 19 patients with cluster headache, the mean number of cluster headaches per day decreased from 4.5 attacks to 2.6 attacks at 1-year follow-up (p<0.0005)[2].

Acute treatment of pain

In the case series of 19 patients with cluster headache, complete resolution of pain was achieved in 47% of cluster headache attacks within a mean of 11 minutes of starting neurostimulation[2].

Use of rescue medication

In the randomised controlled trial of 97 patients with cluster headache treated by standard care plus tVNS or standard care alone, the mean number of times subcutaneous sumatriptan was used decreased from 7.2 to 2.8 in the standard care plus tVNS group (n=32; p=0.007) and increased from 6.8 to 7.5 in the standard care alone group (n=42; not significant), during the last 2 weeks of a 4-week follow-up period. In the same study, the mean number of times inhaled oxygen was used decreased from 17.3 to 6.5 in the standard care plus tVNS group (n=32; p=0.02) and from 12.6 to 10.8 in the standard care alone group (n=42; not significant) during the last 2 weeks of a 4-week follow-up period[1].

In a case series of 19 patients with cluster headache, a reduction in the use of oxygen inhalation was reported in 75% (12/16) of patients. Of these patients, 2 patients who were using oxygen inhalation as their only acute treatment, stopped using the treatment and preferred to use the tVNS device as their only acute treatment. In the same study, a reduction in the use of triptans was reported in all patients who used triptans: 4 stopped treatment altogether (3 of whom continued to used oxygen inhalation) and 9 reduced their triptan use by a mean of 48±6%[2].

Quality of life

In the randomised controlled trial of 97 patients with cluster headache treated by standard care plus tVNS or standard care alone, mean EQ-5D scores (ranging from 0 to 100 with higher scores indicating better quality of life) increased from baseline by 9.20 and 0.27 points respectively at 4-week follow-up (p=0.039). During the extension phase of the study, patients from both groups received adjunctive tVNS for 4 additional weeks. In this period, mean EQ-5D scores increased from baseline by 10.79 points in patients who were initially in the standard care plus tVNS group and 4.36 points in patients initially in the standard care alone group (p value not reported)[1].

Efficacy of transcutaneous stimulation of the cervical branch of the vagus nerve for treating migraine

Acute treatment of pain

In a case series of 50 patients with high-frequency episodic migraine or chronic migraine, pain relief (defined as more than a 50% improvement in visual analogue scale scores for pain) was reported in 38% (50/131) of attacks, 1 hour after neurostimulation. Complete resolution of pain was reported in 18% (23/131) of attacks, 1 hour after neurostimulation. Pain relief and complete resolution of pain were reported in 51% (67/131) and 23% (30/131) of attacks, respectively, 2 hours after neurostimulation[3].

In a case series of 30 patients with migraine, pain relief (defined as moderate to severe pain at baseline that reduced to mild or no pain) was reported in 43% (23/54) of moderate to severe attacks 2 hours after neurostimulation. In the same study, complete resolution of pain was reported in 22% (12/54) of moderate to severe attacks 2 hours after neurostimulation. Complete resolution of pain was reported in 38% (10/26) of mild attacks 2 hours after neurostimulation[4].

Improvements of associated symptoms

In the case series of 50 patients with high-frequency episodic migraine or chronic migraine, relief of nausea was reported in 66% (87/131) of attacks 2 hours after neurostimulation. The authors did not report the number of attacks that were accompanied by nausea. In the same study, relief of photophobia was reported in

76% (100/131) of attacks and relief of phonophobia was reported in 77% (101/131) of attacks 2 hours after neurostimulation[3].

In the case series of 30 patients with migraine, relief of nausea was reported in 38% (11/29) of attacks which were accompanied by nausea. In the same study, relief of photophobia was reported in 30% (16/53) of attacks which were accompanied by photophobia. Relief of phonophobia was reported in 52% (17/33) of attacks which were accompanied by phonophobia[4].

Recovery from functional disability

In the case series of 50 patients with high-frequency episodic migraine or chronic migraine, complete recovery from functional disability was reported in 35% (46/131) of attacks 2 hours after neurostimulation[3].

Need for rescue medication

In the case series of 50 patients with high-frequency episodic migraine or chronic migraine, rescue medication was needed in 53% (70/131) of attacks 2 hours after neurostimulation[3].

Safety

Induction or worsening of headache

In a randomised controlled trial of 97 patients with cluster headache transcutaneous vagus nerve stimulation (tVNS) was judged to cause cluster headache in 2% (1/48) of patients in the standard care plus tVNS group and 10% (5/49) of patients initially in the standard care alone group but who then received adjunctive tVNS in a 4-week extension phase. In the same study, headaches that were not cluster headaches were reported in 8% (4/48) of patients in the standard care plus tVNS group and 2% (1/49) of patients initially in the standard care alone group[1].

Transient worsening of headache was reported in 1 patient in a case series of 19 patients with cluster headache[2].

Dizziness

Dizziness was reported in 6% (3/48) of patients in the standard care plus tVNS group and 6% (3/49) of patients in the standard care alone group in the randomised controlled trial of 97 patients with chronic cluster headache (no further details on timing in relation to tVNS provided)[1].

Mild or moderate dizziness was reported in 7% (2/28) of patients in a case series of 30 patients with migraine. Symptoms lasted for up to 1 hour in 1 patient[4].

Muscular pain

Neck pain was reported in 6% (3/48) of patients in the standard care plus tVNS group and no patients in the standard care-alone group in the randomised controlled trial of 97 patients with chronic cluster headache[1].

Oropharyngeal pain was reported in 6% (3/48) of patients in the standard care plus tVNS group and 2% (1/49) of patients in the standard care alone group in the randomised controlled trial of 97 patients with chronic cluster headache[1].

Moderate shoulder pain or spasm was reported in 7% (2/28) of patients in the case series of 30 patients with migraine (no further details on timing in relation to tVNS provided)[4].

Facial drooping

Mild lip or facial drooping was reported in 7% (2/28) of patients in the case series of 30 patients with migraine (no further details on timing in relation to tVNS provided)[4].

Neck stiffness

Neck stiffness was reported in 18% (5/28) of patients in the case series of 30 patients with migraine (no further details on timing in relation to tVNS provided)[4].

Skin irritation

Reddening of the skin around the treatment site was reported in 7% (2/28) of patients in the case series of 30 patients with migraine[4].

Nasopharyngitis

Nasopharyngitis was reported in 2% (1/48) of patients in the standard care plus tVNS group and 8% (4/49) of patients in the standard care-alone group in the randomised controlled trial of 97 patients with chronic cluster headache[1].

Urination

Frequent urination was reported in 14% (4/28) of patients in the case series of 30 patients with migraine[4].

Other adverse events

In the randomised controlled trial of 97 patients with chronic cluster headache treated by standard care plus tVNS or standard care alone, 1 or more of the following device-related adverse events were reported in 27% (13/48) of patients in the standard care plus tVNS group: depressed mood, malaise, oropharyngeal

pain, induced cluster headache, muscle twitching, muscle spasms, hot flushes, acne, pain, throat tightness, dizziness, hyperhidrosis, toothache, decreased appetite and skin irritation. One or more of the following device-related adverse events were reported in 14% (7/49) of patients initially in the standard care alone group: erythema, facial oedema, induced cluster headache, chest pain, fatigue, depressed mood, pruritus, musculoskeletal stiffness and parosmia. All adverse events occurred during the extension phase of the study when these patients received adjunctive tVNS[1].

A single occurrence of the following adverse events was reported in the case series of 30 patients with migraine: mild confusion that lasted for 2 hours after neurostimulation, joint pain, mild twitching of neck muscles, mild swelling of the neck, tinnitus in 1 ear, fever (39ºC), a raspy voice, fatigue, coughing and sneezing[4].

Palpitations were reported in 1 patient in a case series (conference abstract) of 18 patients with various primary headache disorders. In the same study, tonic muscle contraction was reported in 17% (3/18) of patients and cervical muscle spasm was reported in 1 patient[5].

Validity and generalisability of the studies

- No studies were identified that evaluated the safety or efficacy of tVNS for treating medication overuse headache.
- Literature searches only identified 1 randomised controlled trial. The study compared the efficacy of adjunctive tVNS against standard care alone for treating cluster headache[1].
- No comparative studies were identified that compared tVNS against acute or prophylactic medications for treating migraine.
- Most participants in the cluster headache studies were male[1,2] whereas most participants in the migraine studies were female[3,4].
- The longest follow-up period reported was 1 year[2].
- Stimulation durations varied across studies.

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

- Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache. NICE interventional procedure guidance 527 (2015). Available from http://www.nice.org.uk/guidance/ipg527
- Transcranial magnetic stimulation for treating and preventing migraine. NICE interventional procedure guidance 477 (2014). Available from http://www.nice.org.uk/guidance/ipg477
- Occipital nerve stimulation for intractable chronic migraine. NICE interventional procedure guidance 452 (2013). Available from http://www.nice.org.uk/guidance/ipg452
- Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedure guidance 381 (2011). Available from http://www.nice.org.uk/guidance/ipg381
- Vagus nerve stimulation for treatment-resistant depression. NICE interventional procedure guidance 330 (2009). Available from http://www.nice.org.uk/guidance/ipg330

NICE guidelines

- Headaches in over 12s: diagnosis and management. NICE guideline 150 (2012). Available from http://www.nice.org.uk/guidance/cg150

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 is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Five Specialist Advisor Questionnaires for transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine were submitted and can be found on the NICE website [INSERT HYPER LINK TO MAIN IP PAGE].

Patient commentators' opinions

NICE's Public Involvement Programme sent 42 questionnaires to 5 NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 22 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Issues for consideration by IPAC

Ongoing trials:

- NCT02378844: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of the gammaCore®, a Non-invasive Neurostimulator Device, for the Prevention of Episodic Migraine; Study type, randomised controlled trial; location, United States; estimated enrolment, 400; estimated completion date, December 2016.
  NCT01701245: A Randomized, Multicenter Study for the Prevention and Acute Treatment of Chronic Cluster Headache Using Gammacore, Versus Standard of Care; Study type, randomised controlled trial; location, United States; estimated enrolment, 80; estimated completion date, January 2014. However, the study is currently recruiting patients, according to the clinical trials website.

References

1. Gaul C, Diener HC, Silver N et al. (2015) Non-invasive vagus nerve stimulation for prevention and acute treatment of chronic cluster headache (PREVA): a randomised controlled trial. Cephalalgia 0(0) 1–13. doi: 10.1177/0333102415607070
2. Nesbitt AD, Marin JC, Tompkins E et al. (2015) Initial use of a novel non-invasive vagus nerve stimulator for cluster headache treatment. Neurology 84 (12): 1249-53. doi: 10.1212/WNL.0000000000001394.
3. Barbanti P, Grazzi L, Egeo G et al. (2015) Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. The Journal of Headache and Pain. 16:542. doi: 10.1186/s10194-015-0542-4.
4. Goadsby PJ, Grosberg BM, Mauskop A et al. (2014) Effect of non-invasive vagus nerve stimulation on acute migraine: an open-label pilot study. Cephalalgia 34 (12): 986-93. doi: 10.1177/0333102414524494.
5. Magis D, Gerard P and Schoenen P. (2013) Transcutaneous Vagus Nerve Stimulation (tVNS) for headache prophylaxis: initial experience. The Journal of Headache and Pain 14 (Suppl 1): P198.

Appendix A: Additional papers on transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine

There were no additional papers identified.

Appendix B: Related NICE guidance for transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine

Guidance	Recommendations
Interventional procedures	**Vagus nerve stimulation for treatment-resistant depression. NICE interventional procedure guidance 330 (2009)** 1.1 Current evidence on the safety and efficacy of vagus nerve stimulation (VNS) for treatment-resistant depression is inadequate in quantity and quality. Therefore this procedure should be used only with special arrangements for clinical governance, consent and audit or research. It should be used nly in patients with treatment-resistant depression. 1.2 Clinicians wishing to undertake VNS for treatment-resistant depression should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and/or their parents/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. • Audit and review clinical outcomes of all patients having VNS for treatment-resistant depression (see section 3.1). 1.3 Patient selection and management should be carried out by a multidisciplinary team including a psychiatrist and a surgeon (usually a neurosurgeon), with other relevant specialists (for example, a clinical psychologist and an appropriately trained technician). 1.4 NICE encourages further research into VNS for treatment-resistant depression. Research outcomes should include depression rating scales, objective measures of depressive symptoms and patient-reported quality of life. NICE may review the procedure on publication of further evidence. **Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache. NICE interventional procedure guidance 527 (2015)** Current evidence on the efficacy of implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache, in the short term (up to 2 months), is adequate. With regard to safety, a variety of complications have been documented, most of which occur early and resolve; surgical

	revision of the implanted system is sometimes needed. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to implant a sphenopalatine ganglion stimulation device for chronic cluster headache should: • Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the uncertainty about the procedure's safety and long‑term efficacy and provide them with clear written information. Patients should be informed about other treatment options. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients having sphenopalatine ganglion stimulation (see section 7.2). 1.3 The selection of patients for implantation of a sphenopalatine ganglion stimulation device and their management should be done by multidisciplinary teams specialising in refractory headache. 1.4 Clinicians should enter details about all patients being implanted with a sphenopalatine ganglion stimulation device onto the national Neuromodulation register hosted by the National Institute for Cardiovascular Outcomes Research (NICOR). Clinical outcomes should also be reviewed locally. 1.5 NICE encourages further research on sphenopalatine ganglion stimulation for chronic cluster headache. Reported outcomes should include long‑term efficacy and device durability. **Occipital nerve stimulation for intractable chronic migraine. NICE interventional procedure guidance 452 (2013).** 1.1 The evidence on occipital nerve stimulation (ONS) for intractable chronic migraine shows some efficacy in the short term but there is very little evidence about long‑term outcomes. With regard to safety, there is a risk of complications, needing further surgery. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. 1.2 Clinicians wishing to undertake ONS for intractable chronic migraine should take the following actions: • Inform the clinical governance leads in their Trusts.

	• Ensure that patients 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 the public is recommended. 1.3 Selection of patients for treatment using ONS for intractable chronic migraine should be done by a multidisciplinary team, including specialists in headache, pain management and neurosurgery. 1.4 Clinicians should enter details about all patients undergoing ONS for intractable chronic migraine onto the UK Neuromodulation Register when access to that database is available. They should audit and review clinical outcomes locally and should document and consider their relationship to patient characteristics. 1.5 NICE encourages publication of further information from comparative studies and from collaborative data collection to guide future use of this procedure and to provide patients with the best possible advice. Publications should include full details of any complications, and of adjunctive or subsequent treatments. Outcomes should include measures of pain, function and quality of life, particularly in the long term. 1.6 NICE may review the procedure on publication of further evidence. **Transcranial magnetic stimulation for treating and preventing migraine. NICE interventional procedure guidance 477 (2014).** 1.1 Evidence on the efficacy of TMS for the treatment of migraine is limited in quantity and for the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate but there is uncertainty about the safety of long-term or frequent use of TMS. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Patient selection should normally be done in specialist headache clinics and the procedure should only be used under the direction of clinicians specialising in the management of headache. 1.3 Patients should be informed that TMS is not intended to provide a cure for migraine and that reduction in symptoms may be modest. 1.4 Clinicians wishing to undertake TMS for treating and preventing migraine should take the following actions. • Inform the clinical governance leads in their NHS

	trusts. • Ensure that patients 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 the public is recommended. • Audit and review clinical outcomes of all patients having TMS for the treatment and prevention of migraine (see section 7.1). 1.5 NICE encourages further research on TMS for treating and preventing migraine. Data should be collected for all patients not entered into controlled trials. Studies should describe clearly whether its use is for treatment or prevention. They should report details of patient selection and the dose and frequency of use. Outcome measures should include the number and severity of migraine episodes, and quality of life in both the short and long term. The development of any neurological disorders (such as epilepsy) in the short or longer term after starting treatment should be documented. **Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedure guidance 381 (2011).** 1.1 Current evidence on the efficacy of deep brain stimulation (DBS) for intractable trigeminal autonomic cephalalgias (TACs) is limited and inconsistent, and the evidence on safety shows that there are serious but well-known side effects. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake DBS for intractable TACs should take the following actions: • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy. They should be specifically informed that DBS may not control their headache symptoms and they should be fully informed about the possible risks associated with the procedure, including the small risk of death. Clinicians should provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having DBS for intractable TACs (see section 3.1). 1.3 Patient selection for DBS for intractable TACs should be carried out by a multidisciplinary team specialising in pain management.

	1.4 Further research studies should clearly define patient selection and report the intensity and duration of stimulation, medication use and quality of life, in addition to documenting the effects on headache symptoms as clearly as possible.
NICE guidelines	**Headaches in over 12s: diagnosis and management. NICE clinical guideline 150 (2012).** **1.3 Management** **Cluster headache** **Acute treatment** 1.3.26 Discuss the need for neuroimaging for people with a first bout of cluster headache with a GP with a special interest in headache or a neurologist. 1.3.27 Offer oxygen and/or a subcutaneous or nasal triptan for the acute treatment of cluster headache. 1.3.28 When using oxygen for the acute treatment of cluster headache: • use 100% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag and • arrange provision of home and ambulatory oxygen. 1.3.29 When using a subcutaneous or nasal triptan, ensure the person is offered an adequate supply of triptans calculated according to their history of cluster bouts, based on the manufacturer's maximum daily dose. 1.3.30 Do not offer paracetamol, NSAIDS, opioids, ergots or oral triptans for the acute treatment of cluster headache. **Prophylactic treatment** 1.3.31 Consider verapamil for prophylactic treatment during a bout of cluster headache. If unfamiliar with its use for cluster headache, seek specialist advice before starting verapamil, including advice on electrocardiogram monitoring. 1.3.32 Seek specialist advice for cluster headache that does not respond to verapamil. 1.3.33 Seek specialist advice if treatment for cluster headache is needed during pregnancy.

Appendix C: Literature search for transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	11/08/15	Issue 7 of 12, July 2015
Cochrane Central Database of Controlled Trials - CENTRAL	11/08/15	Issue 7 of 12, July 2015
HTA database (Cochrane)	11/08/15	Issue 7 of 12, July 2015
MEDLINE (Ovid)	11/08/15	1946 to July Week 5 2015
MEDLINE In-Process (Ovid)	11/08/15	August 10, 2015
EMBASE (Ovid)	11/08/15	1974 to 2015 Week 32
PubMed	11/08/15	-
BLIC (British Library)	11/08/15	-
JournalTOCS [for update searches only]	11/08/15	-

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

1	exp Cluster Headache/
2	(clust* adj4 headach*).tw.
3	exp Migraine Disorders/
4	Migrain*.tw.
5	((daily* or chron* or persist* or constant* or recur* or intract*) adj4 headach*).tw.
6	Headache Disorders/
7	(Headach* adj4 (disord* or syndrom*)).tw.
8	exp Trigeminal Autonomic Cephalalgias/
9	(Trigemin* adj4 Autonom* adj4 cephalalg*).tw.
10	TACs.tw.
11	(medicat* adj4 overuse adj4 head*).tw.
12	or/1-11
13	Vagus nerv* stimulat*.tw.

14	Vagus Nerve Stimulation/
15	Electric Stimulation Therapy/
16	(Elect* adj4 stimulat* adj4 therap*).tw.
17	Neuromodulat*.tw.
18	neurostimulati*.tw.
19	((Sphenopalatin* or pterygopalat* or Meckel*) adj4 stimulat*).tw.
20	Transcutaneous Electric Nerve Stimulation/
21	(Transcutane* adj4 Electr* adj4 nerv* adj4 Stimulat*).tw.
22	(implant* adj4 (stimulat* or electrod*)).tw.
23	Electrodes, Implanted/
24	(Electrod* adj4 implant*).tw.
25	or/13-24
26	12 and 25
27	Gammacore.tw.
28	NEMOS.tw.
29	Cefaly.tw.
30	26 or 27 or 28 or 29
31	animals/ not humans/
32	30 not 31