Transcutaneous vagus nerve stimulation for treatment of cluster headache and migraine

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Summary

- The vagus nerve is a complex cranial nerve with a variety of functions. Experience with implanted electrical stimulation devices for the treatment of epilepsy suggested that vagus nerve stimulation may be helpful for people with cluster headache and migraine.

- gammaCore (electroCore LLC) is a handheld device which provides non-invasive transcutaneous vagus nerve stimulation (nVNS). It is intended for treatment of adults with primary headache, including migraine and cluster headache, and medication overuse headache.

- NICE have issued guidance, which recommends that nVNS should only be used with special arrangements for clinical governance, consent and audit or research.

- One RCT assessed nVNS for prophylaxis of cluster headache. The nVNS group had greater reductions in cluster headache frequency than standard care alone (-5.9 vs. -2.1 attacks/week) and were more likely to reduce attack frequency by at least half (40% vs. 8.3%). Quality of life and headache impact scores were significantly improved.

- Another RCT for acute treatment of cluster headache found no difference in cluster headache pain intensity when nVNS was compared to sham nVNS. A subgroup analysis suggested there may be a significant benefit in patients with episodic, but not chronic, cluster headache.

- One double-blind sham-controlled RCT assessed nVNS for treatment and prophylaxis of migraine. The trial found no difference between groups in the mean number of monthly headache days.

- Several smaller, non-randomised studies have been conducted for both indications, but add little to the available evidence on effectiveness. Limitations of the randomised trials, such as incomplete blinding and short duration, mean that their results should be interpreted with caution.

- Treatment with nVNS appears safe and well-tolerated. The longest-term safety data come from a very small (n=19) 52-week cohort study in patients with cluster headache. There are theoretical safety concerns due to the diverse functions of the vagus nerve, but experience with implanted devices suggests no excess of adverse events.

- Treatment with gammaCore costs £225 per patient per month, with a two month free trial offered by the manufacturer. A German cost-effectiveness analysis suggests that this is cost-effective in cluster headache patients but no UK analyses are available. Drug costs are lower in the UK than those quoted in the analysis, which may alter the cost-effectiveness.
Introduction and background

The vagus nerve is the tenth cranial nerve, and it has a variety of functions. It comprises both afferent fibres (conveying information from the pharynx, larynx, trachea, oesophagus, and viscera to the brain and spinal cord) and motor fibres which innervate the palate, pharynx and larynx. Parasympathetic ("rest and digest") fibres innervate the parotid gland, heart, and abdominal viscera. Implantable vagus nerve stimulation (VNS) devices have been available in Europe and the USA since the 1990s. These are small, surgically implanted devices which provide direct electrical stimulation to the vagus nerve. Originally intended for treatment of epilepsy, the devices were also found to produce improvements in mood, migraine, cluster headache, Alzheimer's disease, heart failure, and anxiety disorders. Implantable VNS were approved in the USA for treatment of recurrent or chronic depression, but not for other conditions. This is due in part to the safety profile, including adverse events related to surgical implantation.

Non-invasive transcutaneous stimulation of the vagus nerve (nVNS) is a newer treatment modality which aims to treat headache disorders while avoiding the need for an implanted device. The mechanism by which nVNS treats headache is poorly understood, but may be due at least in part to inhibition of pain signalling by the neurotransmitter gamma amino butyric acid (GABA).

Cluster headache

Cluster headaches are characterised by recurrent attacks of unilateral pain, often in or around the eye or temple. Attacks usually last between 15 minutes and 3 hours, and are almost invariably described by patients as the worst pain they have ever experienced. Attacks may be episodic (occur in clusters of 1 week to 1 year, separated by remission lasting at least 1 month) or chronic (remission is absent or lasts less than 1 month). The prevalence of cluster headache is roughly 0.2%, and it is at least 2.5 times more common in men than in women.

Triptans are recommended for the acute treatment of cluster headache. Subcutaneous sumatriptan is licensed for this indication and is the most rapid and effective treatment. Sumatriptan or zolmitriptan nasal sprays may be used in people who are unable or unwilling to use subcutaneous treatment, but are not licensed. Simple analgesics such as NSAIDs, aspirin or paracetamol should not be offered since there is no evidence that they are helpful. Patients should also be provided with home and ambulatory oxygen therapy; 100% oxygen at a rate of at least 12 litres/min is indicated for patients unless they have COPD. Prophylactic treatment with verapamil should be considered.

Migraine

Migraine is a primary headache disorder characterised by episodic headaches accompanied by other symptoms such as photophobia, phonophobia, nausea and vomiting. Migraine is often accompanied by aura, which commonly features positive or negative visual phenomena. Migraine is much more common than cluster headache, with a prevalence of around 18% in women and 6% in men.
Treatment of migraine involves pharmacological intervention plus lifestyle advice. Known triggers should be avoided, but it is acknowledged that triggers are often not identifiable or avoidable. Acute treatment with an oral triptan and/or NSAIDs should be the first choice of treatment, with consideration given to adding an anti-emetic. Preventive treatment can be considered if migraines are causing frequent disability, or in patients at risk of medication overuse headache. Options for migraine prophylaxis include topiramate and propranolol. Other drugs are in routine use, but there is no good evidence for efficacy; these include amitriptyline, venlafaxine, lisinopril, sodium valproate and angiotensin receptor antagonists.\(^5\)

**The gammaCore device**

GammaCore (electroCore LLC) is a handheld device approximately the size of a mobile phone. It produces a proprietary electrical signal which consisting of a 5 kHz sine wave series which lasts 1 millisecond and repeats every 40 milliseconds. The device delivers a peak of 24 volts and 60 milliamps. The stimulation amplitude can be adjusted by the user to achieve a level of stimulation which is effective without being overly painful. The device provides audio and visual feedback to allow easy adjustment of treatment intensity. GammaCore has two stainless steel contact surfaces which, together with conductive gel, are applied to the right side of the neck. The device produces a tingling or prickling sensation at the application site, alongside muscle twitching, but should not cause real discomfort.\(^6\)

GammaCore is intended for the treatment of adults with primary headache (including migraine, cluster headache, and hemicranias continua) and medication overuse headache. It is contraindicated in patients with any implantable device such as a metal plate or screw near the treatment site, a pacemaker, hearing aid, or any other electronic device. It should not be used by patients with diagnosed carotid atherosclerosis, a history of cervical vagotomy, or with any open wound, rash, or lesion at the treatment site. It must not be used on wet skin.

This document will review the evidence for the effectiveness and cost-effectiveness of gammaCore for the treatment of cluster headache and migraine.

**Guidance and related advice**

NICE published interventional procedure guidance on the use if non-invasive vagus nerve stimulation in March 2016. The guidance does not name any specific products but does state that it applies to handheld devices applied to the neck. In the UK, this definition currently applies only to gammaCore.

NICE found that there was no evidence of substantial safety concerns, but that the evidence for efficacy was limited. They therefore recommended use of nVNS only with special arrangements for clinical governance, consent, and audit or research. Further research is encouraged. The guidance has no information on cost or cost-effectiveness.\(^7\)
Clinical efficacy – cluster headache

Prophylaxis

The Prevention and Acute Treatment of Chronic Cluster Headache (PREVA) trial was an open-label RCT which compared the gammaCore device plus individualised standard care to standard care alone.8 The randomised treatment period lasted 4 weeks, and there was a 2 week baseline period during which all patients received only standard care. There was also an optional 4 week extension phase, during which all patients received nVNS plus standard care.

Participants were adults aged 18 to 70 years with a history of ≥1 year of chronic cluster headache according to the International Classification of Headache Disorders (ICHD) criteria prior to enrolment. Exclusion criteria included any changes to prophylactic medications <1 month prior to enrolment, history of intracranial or carotid aneurysm or haemorrhage, brain tumours or lesions, previous surgery or abnormal anatomy at the treatment site, cardiovascular disease, implantation with any electrical devices, neurostimulation devices or metallic hardware, and recent history of syncope or seizure.

Patients using gammaCore were instructed to use it prophylactically. The treatment schedule specified three stimulations (lasting two minutes each) were to be given within one hour of waking each day, with five minutes between each dose. This was to be repeated 7-10 hours later, for a total of 6 doses each day. Participants were also able to use gammaCore for acute treatment of attacks, if desired. In this case three doses were to be used at the onset of headache, and routine prophylactic doses should not be taken within 2 hours after acute use. If headache was not aborted 15 minutes after acute use of gammaCore participants were instructed to take abortive medications.

The primary endpoint was reduction in the mean number of cluster headache attacks each week, defined as the mean number of attacks during the last two weeks of the study minus the number of attacks during the baseline period, divided by two. Information on headaches was captured by patient-completed headache diaries which recorded the number of attacks, pain intensity (on a 5-point scale of none to very severe), headache duration, and use of abortive drugs.

Secondary endpoints included the proportion of patients with ≥50% reduction in mean attacks, use of abortive medicines, duration and intensity of attacks acutely treated with gammaCore and health-related quality of life (HRQoL).

A total of 97 patients were randomised to treatment. Participants had a mean age of 42-45 years, and around two thirds were men. The mean number of weekly cluster headache attacks at baseline was 16.8 per week in the nVNS group and 18.5 per week in the control arm. The most commonly-used prophylactic medicines were verapamil (53%), lithium (15%), and topiramate (14%). Four patients (4%) used corticosteroids prophylactically. For acute treatment of cluster headache attacks, 90% of patients used pharmacologic interventions and around two thirds used oxygen.

A total of 64.4% of patients assigned to nVNS had ≥80% adherence during the randomised phase. There was a greater mean reduction in headache attacks in the nVNS group than with standard care alone (see table 1 below). Outcomes at the end of the extension phase were similar. The majority of patients (94%) chose to use nVNS as abortive therapy during at least one attack, but this had no effect on the overall duration or intensity of attacks.
HRQoL was assessed using the EQ-5D-3L index score, which produces a value from 0 (death) to 1 (perfect health). A change of 0.074 (7.4%) is considered the minimum important difference. The change in quality of life in the nVNS arm exceeded this value.

Headache disability was assessed using the Headache Impact Test (HIT-6) questionnaire. HIT-6 asks patients to answer six questions, covering domains such as pain and impact on daily activities or work, on a scale of “never” to “always”. It produces a numeric score from 36 (no impact) to 78. Scores above 60 are considered to represent very severe impact. The minimally important difference is estimated at between 2.4 and 2.7 points. The change in HIT-6 scores in the nVNS arm exceeded this value.

**Table 1. Outcomes of the PREVA trial during the randomised phase**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>nVNS (n=45)</th>
<th>Standard care (n=48)</th>
<th>Treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack frequency at baseline</td>
<td>16.8</td>
<td>18.5</td>
<td>-</td>
</tr>
<tr>
<td>Reduction in mean attack frequency*</td>
<td>-5.9</td>
<td>-2.1</td>
<td>3.9 (95% CI 0.5 to 7.2, p=0.02)</td>
</tr>
<tr>
<td>≥50% response rate</td>
<td>40%</td>
<td>8.3%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Abortive medication use</td>
<td>-15 (-22.8 to -7.2, p&lt;0.001)</td>
<td>-2 (-9.4 to 5.4, p=0.6)</td>
<td>-</td>
</tr>
<tr>
<td>Change in EQ-5D-3L</td>
<td>0.145</td>
<td>-0.049</td>
<td>0.194 (95% CI 0.054 to 0.334, p=0.007)</td>
</tr>
<tr>
<td>Change in HIT-6 scores</td>
<td>-2.78</td>
<td>-0.47</td>
<td>-</td>
</tr>
</tbody>
</table>

**Limitations**

The trial is limited by its open-label design and short duration. Sham devices, as used in other trials, had not yet been developed when this trial was conducted.

Efficacy analyses were conducted in the intention-to-treat (ITT) population, which in this trial was defined as all patients who recorded at least one efficacy recording in their headache diary after randomisation. Four patients randomised to the treatment arm and one assigned to standard care alone treatment were excluded from the ITT population. A true ITT analysis should include all randomised participants, regardless of adherence, withdrawal or deviation from protocol. Failure to use this definition, as in this trial, means that study outcomes may be less conservative and less reflective of a real-world population.

**Acute treatment**

The ACT1 study was a randomised, double-blind clinical trial which compared nVNS to sham nVNS for the acute treatment of cluster headache attacks. The sham
device was identical to the active device, but supplied only a low-frequency biphasic signal that did not stimulate the vagus nerve. Participants were adults aged 18 to 75 with a diagnosis of cluster headache according to ICHD criteria; exclusion criteria were similar to those described above.

The trial had a randomised phase which lasted either one month or until five headache attacks had been treated, whichever was shorter. This was followed by an open-label phase during which all patients received three months of active nVNS treatment.

Patients were instructed to use their nVNS (or sham) device for three consecutive two minute applications at the first sign of a headache attack. The device could only be used once in any 12 hour period, and abortive medicines could be used 15 minutes after each nVNS treatment.

The primary outcome was response rate for the first treated cluster headache attack. Response was defined as the proportion of patients who achieved a pain intensity score of 0 or 1 within 15 minutes of treatment initiation. Pain was rated on a 5 point scale from 0 (no pain) to 4 (very severe pain). Use of rescue medication within 60 minutes was considered treatment failure. Secondary outcomes included sustained treatment response and mean pain intensity scores at 15 minutes. Data were collected using patient-reported headache diaries.

A total of 150 patients were enrolled and randomised, of whom 128 completed the double-blind phase and entered the open-label extension. The mean age was around 48 years, 84% of participants were men, and patterns of drugs for prophylaxis and acute treatment of cluster headaches were similar to the above trial. Two thirds of patients had episodic cluster headache while the remainder had the less common chronic variant.

Response rates were not significantly different with nVNS than sham treatment in the overall study population (see table 2 below). Subgroup analysis found a significant benefit of nVNS in patients with episodic cluster headache, but it is not clear whether this was a pre-specified or post-hoc analysis.

**Limitations**

The sham nVNS device did not cause localised muscle contraction at the application site in the same way as the active device. This may have led to accidental unblinding, and in fact the authors noted that “a considerable proportion of patients correctly guessed their treatment allocation” after one treatment. Levels of unblinding appeared to reduce with further treatment and blinding was successful at the end of the double-blind period. Since the primary outcome was assessed using data from the first attack only this imperfect blinding may have introduced bias.

As with the previous trial, the definition of the ITT population used in this study was not standard. In this trial the ITT population was defined as all patients who treated at least one cluster headache attack with active or sham nVNS. Thirteen patients randomised to the treatment arm and four assigned to sham treatment were excluded from the ITT population.

Power calculations determined that the trial had 82% power at a significance level of p≤0.05, but assumed that response rates would be 50% in the active treatment arm and 25% with sham treatment. Treatment responses during the trial were 26.7% and
15.1% respectively (p=0.1). This means that the trial was likely underpowered; there may have been a true difference in response rates between the treatment arms which the trial was not able to detect.

Table 2. Outcomes of the ACT1 trial

<table>
<thead>
<tr>
<th></th>
<th>nVNS (n=73)</th>
<th>Sham nVNS (n=77)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate</strong> (pain rated 0-1 within 15 minutes, first attack only, primary outcome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>26.7%</td>
<td>15.1%</td>
<td>0.10</td>
</tr>
<tr>
<td>Episodic cluster headache (n=101)</td>
<td>34.2%</td>
<td>10.6%</td>
<td>0.008</td>
</tr>
<tr>
<td>Chronic cluster headache (n=49)</td>
<td>13.6%</td>
<td>23.1%</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Sustained response</strong> (pain rated 0-1 at 15-60 minutes, first attack only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>26.7%</td>
<td>12.3%</td>
<td>0.04</td>
</tr>
<tr>
<td>Episodic cluster headache</td>
<td>34.2%</td>
<td>10.6%</td>
<td>0.008</td>
</tr>
<tr>
<td>Chronic cluster headache</td>
<td>13.6%</td>
<td>15.4%</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Mean pain intensity at 15 minutes</strong> (scale of 0-4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.1</td>
<td>2.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Episodic cluster headache</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Chronic cluster headache</td>
<td>2.3</td>
<td>1.9</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Cohort study**

A small cohort study (n=19) assessed the long-term effectiveness of gammaCore for prophylactic and acute treatment of cluster headache.\textsuperscript{13} Patients used up to three doses to treat headache attacks, in addition to two or three doses morning and afternoon for prophylaxis throughout the 52 week study period. Effectiveness was assessed by patients estimating their perceived overall change in condition.

The study found that 15/19 patients (79%) had fewer headache attacks during treatment compared to baseline. When headaches did occur, participants were able to abort attacks within an average of 11 minutes. Most patients were able to reduce their use of oxygen and triptans. The small size of this study, lack of a control group, and use of estimation to assess efficacy mean that the results should be interpreted very cautiously.

**Clinical efficacy – migraine**

**RCT**

The EVENT study was a randomised, double-blind clinical trial which compared nVNS to sham nVNS for the prevention of migraine.\textsuperscript{14} The sham device was
identical in appearance, weight and visual and audible feedback to the active device, but did not produce any electrical stimulations. Participants (n=59) were adults aged 18 to 65 with a diagnosis of chronic migraine with or without aura according to ICHD criteria, who had experienced ≥15 migraine days per month in the preceding 3 months. Exclusion criteria included known pathology of the head, brain or treatment area, previous surgery at the treatment area, cardiovascular disease, hypertension, implanted electrical devices, use of botox injection in the previous 6 months or use of prophylactic migraine medicines in the previous 30 days. Medicines for acute treatment of headache were permitted.

The treatment regimen consisted of three doses of vagus nerve stimulation lasting two minutes each, separated by 5-10 minutes and delivered within one hour of waking. This was then repeated 6-8 hours after the first treatment, and then again 6-8 hours after the second treatment. The trial consisted of a 1 month baseline phase, a 2 month double-blind phase, and a 6 month open-label extension during which all patients were switched to nVNS treatment.

The primary endpoint was safety and tolerability of the nVNS device. The primary efficacy outcome was number of headache days per 28 days, which was recorded using headache diaries. No power calculations were performed. All outcomes were assessed with ITT analyses, which in this case appeared to utilise a true ITT population consisting of all randomised participants.

Participants had a mean age of around 40 years and were mostly female (90%). Mean treatment adherence was ≥95% in both groups during the double-blind phase and remained high (≥90%) during the open-label period. There was no difference in treatment satisfaction between the active and sham nVNS groups, and most patients found the device somewhat easy or very easy to use. As with the cluster headache trial using a sham device, a significant proportion of patients (approx. 38%) were able to correctly identify their treatment arm during the randomised phase.

**Table 3: Mean change in number of headache days per 28 days**

<table>
<thead>
<tr>
<th></th>
<th>nVNS (n=30)</th>
<th>Sham nVNS (n=29)</th>
<th>Inter-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean headache days per 4 weeks at</td>
<td>20.8</td>
<td>22.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Double blind period (primary efficacy outcome)</td>
<td>-1.4 (95% CI -3.7 to 0.77, p=0.44)</td>
<td>-0.2 (95% CI -1.5 to 1.1, p=0.72)</td>
<td>p=0.35</td>
</tr>
<tr>
<td>Open-label period*</td>
<td>-3.6 (95% CI -6.3 to -0.87, p=0.02)</td>
<td>-2.5 (95% CI -5.0 to -0.04, p=0.06)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*all patients received active nVNS treatment during this phase. Results are presented by original treatment allocation.

There was no significant difference in the mean number of headache days per 4 weeks during the double-blind phase of the trial (see table 3 above). There was a significant reduction from baseline during the open-label period, but lack of comparator or blinding for this phase means that the outcome must be interpreted...
with caution. There was a greater reduction in number of headache days with increased duration of use in the per-protocol population, reaching statistical significance after 4 months. However, small patient numbers limit the usefulness of these data (n=32 at 4 months, reducing to n=15 at 8 months).

As above, the lack of a power calculation for this trial combined with the non-significant primary efficacy outcome means that the trial may have been underpowered to detect any difference between the two treatment groups. Differences observed during the open-label period should be interpreted cautiously due to the possibility of bias.

**Non-randomised studies**

Two small (n=50 and n=30), open-label, single-arm trials have been published.15,16 Both recruited adults with a diagnosis of migraine, and excluded patients with cardiovascular disease, significant neurological or systemic disorder, or with implanted electrical devices.

Patients in the first study were asked to self-treat up to 3 migraine attacks in a 2 week period with 2 x 2 minute doses within 20 minutes of onset. Those in the second trial were asked to self-treat up to 4 migraine attacks in a 6 week period with 2 x 90 second doses, 15 minutes apart, once pain became moderate/severe or after 20 minutes of mild pain.

The participants in both studies were largely female and had a mean age of around 40 years. Data were collected with headache diaries. Both trials found that nVNS treatment resulted in around 22% of patients being pain-free 2 hours after the onset of a migraine attack. The larger trial found that nVNS provided ≥50% reduction in pain in 56.3% of patients after 1 hour, and in 64.6% of patients after 2 hours. These data are difficult to contextualise without any control groups with which to compare.

**Menstrual migraine**

A small (n=56) open-label, single arm study assess gammaCore for the prevention of menstrual migraine.17 Participants were Italian women aged 18-50 with a regular menstrual cycle and >1 year history of migraine and a diagnosis of menstrual or menstrual-related migraine with or without aura. Women who exclusively experience migraine during at least 2/3 menstrual cycles are said to have menstrual migraine, while those who experience migraine during 2/3 menstrual cycles but also at other times are diagnosed with menstrual-related migraine.18 Women with other primary headache disorders (including chronic migraine) were excluded, as were those who had failed treatment with ≥3 classes of prophylactic drugs.

One dose of gammaCore stimulation was applied to each side of the neck, and this procedure was repeated three times daily. The device was used starting 3 days before the estimated start of menstruation until 3 days after the end of menstruation, for an average treatment duration of 10-14 days per month. Prophylactic medicines were allowed as long as the doses were stable. Participants were also allowed to use their usual acute analgesics for any migraines that occurred during the study, which lasted 12 weeks. The primary endpoint was the mean change in number of days of days per month with menstrual migraine. Data were collected with headache diaries.
Enrolled women had a mean age of 40 years and a mean age of migraine onset of 18. Most women (91%) had menstrual-related migraine. The mean number of migraine days decreased from 7.2 days at baseline to 4.7 days at the end of treatment (p<0.001). Twenty women (39%) had a ≥50% reduction in the mean number of migraine days. Mean analgesic use decreased from 8.9 to 5.6 times per month (p<0.001). There was a small reduction in mean pain intensity, from 7.6 at baseline to 7.1 at the end of treatment (p=0.002) but no difference in allodynia scores (p=0.58).

Quality of life was assessed using the HIT-6 questionnaire. HIT-6 scores improved from a mean of 67.3 at baseline to 64.1 at the end of treatment (treatment difference 3.1, p<0.001). The minimally important difference in HIT-6 scores is estimated at between 2.4 and 2.7 points.  

**Ongoing trials**

One double-blind RCT is ongoing. This trial is comparing gammaCore with a sham device for the prevention of episodic migraine in adults who experience 5-12 migraines per month. The trial has an estimated enrolment of 400 people and is expected to be completed in June 2017.

**Safety**

No major safety concerns were raised by any of the trials discussed, and all adverse events were in line with those reported in the product literature. In trials with a control group, rates of adverse events were generally similar across treatment arms. Common adverse events associated with nVNS included tingling or prickling at the treatment site, treatment site reactions such as erythema, pain in the oropharynx or neck and twitching in the face or neck. Most reported events were mild or moderate in severity; serious events were uncommon.

The small cohort study of nVNS for cluster headache provided the most long-term safety data, at 52 weeks. There were no serious adverse events in this study. Reported events included discomfort due to device use, and mild reactions to the supplied conductive gel. Two patients experienced shifting of their headache from one side to the other. One patient reported worsening cluster headache pain.

There are theoretical safety concerns relating to nVNS treatment, since the vagus nerve has so many functions and innervates a diverse range of organs. Cardiac adverse effects are a particular concern. However, long-term experience with implantable VNS devices used for epilepsy is reassuring, with no evidence of a higher rate of these types of adverse events than in the general population.

**Dosage and administration**

A single 90 second stimulation is considered to constitute one “dose” of vagus nerve stimulation. For prophylaxis of cluster headache and migraine the manufacturers of gammaCore recommend that two doses should be delivered three times daily. Additional doses may be given for acute treatment of headache attacks.
Administration is a multi-step process:6

- Remove any jewellery on the head and neck, including piercings and necklaces.
- Sit comfortably. Locate the treatment site and clean it with alcohol or soap and water.
- Remove the caps from the gammaCore stimulation surfaces, and apply a small amount of conductive gel to each one.
- Turn the device on. When it is ready to use a green light will be displayed and the device will beep once.
- Position the device on the treatment site, using mild to moderate pressure. Increase the stimulation button until the maximum tolerable stimulation level is reached. The device will beep each time the control button is pressed.
- Treat for 90 seconds once the maximum tolerable strength is reached, then remove the device and turn it off. The device will turn off 120 seconds after being switched on.
- Remove leftover conductive gel from the device and neck. Replace the caps.

Cost analysis

Cost-effectiveness – cluster headache

One published analysis used data from the PREVA trial to assess the 1 year cost-effectiveness of gammaCore for acute treatment cluster headache compared with standard care.22 Standard care was individualised and included prophylactic as well as abortive agents. The model used in the analysis was based on the German statutory health insurance perspective.

In the base case, nVNS plus standard care was dominant over standard care alone (see table 4, below). Sensitivity analyses which assessed the effect of loss of treatment response found that nVNS remained dominant to standard care alone.

It should be noted that the acquisition cost for intranasal zolmitriptan and subcutaneous sumatriptan are lower in the UK than the assumptions used for the model (see table 5). This may alter the cost-effectiveness of gammaCore in the UK.
Table 4: results of cost-effectiveness analysis of nVNS for cluster headache

<table>
<thead>
<tr>
<th></th>
<th>nVNS + SoC</th>
<th>SoC alone</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of response</td>
<td>0.489</td>
<td>0.083</td>
<td>-</td>
</tr>
<tr>
<td>Abortive treatments per 14 days:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan (intranasal)</td>
<td>1.6</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>Sumatriptan (SC)</td>
<td>2.8</td>
<td>7.5</td>
<td>-</td>
</tr>
<tr>
<td>Oxygen</td>
<td>6.5</td>
<td>10.8</td>
<td>-</td>
</tr>
<tr>
<td>Cost of gammaCore</td>
<td>€0.87 per dose</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean annual cost*</td>
<td>€7,096.96</td>
<td>€7511.35</td>
<td>-€414.39</td>
</tr>
<tr>
<td></td>
<td>(£6,055.84)</td>
<td>(£6,409.35)</td>
<td>(£353.60)</td>
</tr>
<tr>
<td>QALYs gained per patient</td>
<td>0.607</td>
<td>0.522</td>
<td>+0.085</td>
</tr>
</tbody>
</table>

*UK equivalent costs calculated using exchange rate on 16th Feb 2017.

Table 5: cost per dose of acute treatments for cluster headache

<table>
<thead>
<tr>
<th></th>
<th>Cost used in model</th>
<th>Equivalent in GBP*</th>
<th>Actual UK cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous sumatriptan</td>
<td>€14.07</td>
<td>£12.01</td>
<td>£6.08</td>
</tr>
<tr>
<td>Intranasal zolmitriptan</td>
<td>€31.31</td>
<td>£26.72</td>
<td>£19.75</td>
</tr>
<tr>
<td>Estimated cost of oxygen per headache treated</td>
<td>€2.87</td>
<td>£2.45</td>
<td>Unable to estimate</td>
</tr>
<tr>
<td>gammaCore</td>
<td>€0.87</td>
<td>£0.74</td>
<td>£0.75</td>
</tr>
</tbody>
</table>

*UK equivalent costs calculated using exchange rate on 16th Feb 2017.

Points to consider

The regimen for gammaCore as a prophylactic treatment involves several minutes of use twice daily, including the application of conductive gel. Some patients may find this onerous, which could affect adherence. If used for acute treatment patients will need to carry their gammaCore device with them at all times. While the device is not large or heavy, this may be a nuisance for some. Either prophylactic or acute use may necessitate the use of the device in public for some patients, depending on usual daily activities. This may reduce adherence due to practical considerations or feelings of awkwardness or embarrassment.

These factors will vary with the individual patient. Given that cluster headache and migraine can have substantial impact on quality of life, many may find these inconveniences perfectly acceptable. In the randomised EVENT trial in patients with migraine adherence was ≥95%. In the randomised PREVA trial in people with cluster headache, 64% of patients in the nVNS arm were highly adherent (≥80% adherence) compared with 50% of patients in the standard care only arm. Around two thirds of patients in the PREVA trial would recommend gammaCore to others.8,14 Where treatment satisfaction was reported, around 40-45% of patients were satisfied or very satisfied.14,15
The only long-term safety and efficacy data come from a very small cohort study in patients with cluster headache. The study is reassuring, but more robust long-term data are needed.

As highlighted by NICE in their interventional procedures guidance, cluster headache is an uncommon disorder with limited treatment options while migraine is substantially more common. NICE considered that good evidence of efficacy for migraine is therefore particularly important.7

**Author’s declaration:** The author has no relevant interests to declare.
References

6. electroCore. Instructions for Use for gammaCore-S.
21. Personal communication: electroCore Medical LLC.