



Northern Treatment
Advisory Group

Transcutaneous vagus nerve stimulation for treatment of cluster headache and migraine (update)

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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, cluster headache, and medication overuse headache.
- NICE have issued guidance recommending 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.
- Two RCTs in acute treatment of cluster headache found no difference in cluster headache pain intensity when nVNS was compared to sham nVNS. Subgroup analyses in both trials suggested there may be a significant benefit in patients with episodic, but not chronic, cluster headache. These subgroup analyses must be interpreted with caution.
- 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, short duration, small sample size and low statistical power 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 £[redacted] + VAT per patient for 93 days treatment, with a three month free trial offered by the manufacturer. American and German cost-effectiveness analyses suggest it 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 (tenth cranial nerve) 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.^{1,2}

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.²

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).³

Cluster headache

Cluster headache is a primary headache disorder 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 may be described by patients as the worst pain they have ever experienced. Attacks may be episodic (occur in clusters lasting weeks or months, separated by remission usually lasting months or years) or chronic (attacks occur for a year or more without remission, or remission is absent or lasts less than 1 month). The one-year prevalence of cluster headache is around 0.05%, while the lifetime prevalence is around 0.12%. Episodic cluster headache is the more common form, accounting for 80-90% of cases. The condition is at least 3 times more common in men than in women, for reasons which are not known.^{4,5}

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 12-15 litres/min for 15-20 minutes via a non-rebreather mask is indicated for patients unless they have COPD. Prophylactic treatment with verapamil may be considered.⁵

Migraine

Migraine is another 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, sensory symptoms or

speech/language symptoms. Migraine is much more common than cluster headache, with a prevalence of around 18% in women and 6% in men.^{4,6}

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 plus an NSAID or paracetamol should be the first choice of treatment, although a triptan, NSAID, or aspirin 900mg can be offered if the patient prefers monotherapy. Consideration should be given to adding an anti-emetic, even in the absence of nausea and vomiting. Preventive treatment can be considered if migraines are causing frequent disability, in patients at risk of medication overuse headache, when standard analgesia are not effective or are contraindicated, or for uncommon types of migraine (e.g. hemiplegic migraine). 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.⁶

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.⁷

GammaCore is intended for the treatment of adults with primary headache (including migraine, cluster headache and hemicranias continue) 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 of 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.⁸

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.⁸

Clinical efficacy – cluster headache

Prophylaxis and treatment (chronic cluster headache) – PREVA

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.⁹ 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 $\geq 50\%$ 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 prophylactic. 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 $\geq 80\%$ 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.¹⁰ The minimally important difference is estimated at between 2.4 and 2.7 points.¹¹ The change in HIT-6 scores in the nVNS arm exceeded this value.

Table 1. Outcomes of the PREVA trial after the randomised phase (4 weeks)

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

A post-hoc analysis of the PREVA trial has been published.¹² Endpoints were assessed in a modified intention-to-treat (mITT) population which included only those patients with data available for every study week.

The analysis found that weekly attack frequency in the treatment arm was significantly lower than the standard care arm starting from the second week of randomised treatment and lasting throughout the 4 week extension phase. Patients in the treatment arm were also more likely to experience a reduction in attack frequency of ≥25%, ≥50% (p<0.001) or ≥75% (p=0.009) compared to baseline.

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.

The trial stated that efficacy analyses were conducted in the intention-to-treat (ITT) population. However, in this trial ITT was defined as all patients who recorded at least one efficacy recording in their headache diary after randomisation. A true ITT analysis should include all randomised participants, regardless of adherence, withdrawal or deviation from protocol.¹³ Four patients randomised to the treatment arm and one assigned to standard care alone treatment were excluded from the ITT population. Failure to use this definition means that study outcomes may be less conservative and less reflective of a real-world population.

The post-hoc analysis uses what is described as a modified ITT population, but defined as “subjects who had available data for each study week”. Again, this is less conservative than a true ITT analysis and is likely to have only collected data from the most adherent patients.

Acute treatment (episodic or chronic cluster headache) – ACT1

The ACT1 study was a randomised, double-blind clinical trial which compared nVNS to sham nVNS for the acute treatment of cluster headache attacks.¹⁴ 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 episodic or chronic 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 $p \leq 0.05$, 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 treatments which the trial was not able to detect.

Table 2. Outcomes of the ACT1 trial

	nVNS (95% CI) (n=73)	Sham (95% CI) (n=77)	p value
Response rate (pain rated 0-1 within 15 minutes, first attack only, primary outcome)			
Total cohort	26.7% (16.1 to 39.7)	15.1% (7.8 to 25.4)	0.10
Episodic cluster headache (n=101)	34.2% (19.6 to 51.4)	10.6% (3.6 to 23.1)	0.008
Chronic cluster headache (n=49)	13.6% (2.9 to 34.9)	23.1% (9.0 to 43.7)	0.48
Sustained response (pain rated 0-1 at 15-60 minutes, first attack only)			
Total cohort	26.7% (16.1 to 39.7)	12.3% (5.8 to 22.1)	0.04
Episodic cluster headache	34.2% (19.6 to 51.4)	10.6% (3.6 to 23.1)	0.008
Chronic cluster headache	13.6% (2.9 to 34.9)	15.4% (4.4 to 34.9)	1.0
Mean pain intensity at 15 minutes (scale of 0-4)			
Total cohort	2.1	2.0	0.4
Episodic cluster headache	2.0	2.0	1.0
Chronic cluster headache	2.3	1.9	0.2

Acute treatment (episodic or chronic cluster headache) – ACT2

The ACT2 study was a randomised, double-blind clinical trial which compared nVNS to sham nVNS for the acute treatment of cluster headache attacks.¹⁵ The sham device produced a variable tingling sensation but did not stimulate the vagus nerve. Patients were adults aged ≥ 18 years with a diagnosis of episodic or chronic cluster headache according to ICHD criteria. The trial consisted of a 1 week baseline period, 2 week double-blind treatment phase, and a 2 week open-label extension during which all patients received active nVNS treatment.

Patients were instructed to use their nVNS (or sham) device for three consecutive two minute applications at the time of onset of an attack. Three additional applications could be administered if the attack was not aborted within 9 minutes after the start of the first application. Rescue treatments (medicines and/or inhaled oxygen) were allowed from 15 minutes after the start of the first application. Headache attacks were recorded using paper diaries. Pain was rated on a scale of 0 (no pain) to 4 (very severe pain).

The primary endpoint was proportion of treated attacks which achieved a pain-free status (0 out of 5) within 15 minutes of starting treatment. Secondary endpoints included mean number of attacks with pain scores of 0 or 1 within 30 minutes, mean number achieving pain-free status within 30 minutes, and mean change in pain intensity from 15 to 30 minutes after initiating treatment. The primary safety endpoint was the occurrence of any adverse effects. Outcomes were assessed in the full analysis set (FAS), defined as all randomised patients with at least one post-randomisation efficacy measurement.

There was no difference in the total cohort for the primary endpoint (see Table 3, below). However, as in the ACT1 trial, treatment appeared to be effective in patients with episodic cluster headache.

Table 3. Outcomes of the ACT2 trial

	nVNS	Sham	Odds ratio (95% CI)
Proportion of attacks with pain rated 0 within 15 minutes (primary outcome)			
Total cohort (n=102)	13.5%	11.5%	OR 1.22 (0.42 to 3.51, p=0.71)
Episodic cluster headache (n=30)	47.5%	6.2%	OR 9.19 (1.77 to 47.8, p<0.01)
Chronic cluster headache (n=72)	4.8%	12.9%	OR 0.41 (0.13 to 1.3, p=0.13)
Proportion of attacks with pain rated 0 within 30 minutes			
Total cohort (n=92)	42.7%	27.6%	p=0.05
Episodic cluster headache (n=27)	57.5%	25.5%	p=0.07
Chronic cluster headache (n=65)	36.6%	28.5%	p=0.34
Proportion of attacks with pain rated 0 or 1 within 30 minutes			
Total cohort (n=92)	26.1%	18.3%	p=0.17
Episodic cluster headache (n=27)	43.0%	19.1%	p=0.08
Chronic cluster headache (n=65)	19.2%	17.9%	p=0.76

Limitations

Power calculations determined that the trial had 80% power at an unspecified significance level for the primary outcome, but assumed that response rates would be 60% in the active treatment arm and 30% with sham treatment. Treatment responses during the trial were 13.5% and 11.5% respectively ($p=0.7$). This means that the trial was also likely to be underpowered.

It should be noted that although nVNS treatment appeared to be effective in patients with episodic cluster headache, this was not a pre-specified analysis. As a result, and due to the very small sample size ($n=30$), results should be interpreted very cautiously.

Pooled analysis

A pooled analysis of ACT1 and ACT2 confirmed the findings of the individual trials; nVNS was superior to sham treatment in episodic cluster headache patients only, and not in chronic cluster headache patients or the cohort as a whole.¹⁶

Cohort study

A small cohort study ($n=19$) assessed the long-term effectiveness of gammaCore for prophylactic and acute treatment of cluster headache.¹⁷ 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.¹⁸ 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 $\geq 95\%$ in both groups during the double-blind phase and remained high ($\geq 90\%$) 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

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

*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.^{19,20} 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 $\geq 50\%$ 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.²¹ 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.⁴ 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 $\geq 50\%$ 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.¹¹

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 enrolled 479 people and was expected to be completed in April 2018.²² No results are yet available.

Clinical efficacy – NHS experience

Two small observational studies have examined the efficacy of gammaCore in the NHS. Trimboli et al published the results of a prospective audit of patients treated at the Headache Centre at Guy's and St Thomas' Hospital in London.²³ Patients ($n=41$) had diagnoses of migraine ($n=23$), chronic cluster headache ($n=12$), hemicrania continua ($n=4$) or chronic short-lasting unilateral neuralgiform headache attacks with autonomic symptoms ($n=2$). All were prescribed a three month course of treatment with gammaCore. The audit found:

- All migraine patients had tried at least four classes of prophylactic medicines, and all but one had tried botox. Two patients experienced a reduction of $\geq 30\%$ in headache days, and four had a marginal reduction ($< 30\%$). Seven reported worsening number of headache days and ten reported no change. No patients were able to entirely abort migraines with acute gammaCore use, but two were able to reduce pain severity.
- All cluster headache patients had tried at least three classes of prophylactic medicines; all but one had tried at least four. All patients had tried greater occipital nerve blockade. One patient with chronic cluster headache had a reduction in weekly cluster headache frequency of $\geq 30\%$, and was also able to use less oxygen per week. Two patients had a slight improvement in weekly frequency; one was offered the chance to continue treatment but declined, since they found the device cumbersome to use regularly. Three patients had no change in weekly frequency while six reported worsening.

This is a small study with no control arm, so results should be interpreted cautiously.

Marin et al conducted a retrospective analysis of 30 individual funding requests (IFRs) made to the NHS for use of gammaCore to treat cluster headache.²⁴ Of 30 recruited patients, 29 had chronic cluster headache. After 3-6 months treatment, the mean number of cluster headache attacks reduced from 27.3 per week to 9.8 per week ($p < 0.001$). Mean duration of attacks (53 vs. 25 minutes, $p < 0.001$) and mean severity (7.8 vs. 5.4, $p = 0.003$) were also reduced. As with the above, this was a small uncontrolled study. Additionally the analysis has only been published in abstract form, so full appraisal is not possible.

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.⁷ 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.¹⁷ 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.²⁵

Dosage and administration

The UK information sheet for gammaCore states that a single 90 second treatment is considered to constitute one “dose” of vagus nerve stimulation. For prophylaxis of cluster headache and migraine the manufacturers recommend that two doses should be delivered three times daily. Additional doses may be given for acute treatment of headache attacks.²⁶

Administration is a multi-step process:⁷

- 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

GammaCore costs £■■■ + VAT for 31 days treatment, or £■■■ + VAT for 93 days (£■■■ and £■■■ incl. VAT, respectively). This equates to an annual cost of £■■■ + VAT per patient. The manufacturers offer to provide a 3 month free trial for each patient.²⁶ **This information is confidential to the NHS and commercially sensitive, and should not be disclosed to third parties outside of NTAG.**

Treatment of episodic and chronic cluster headache

A cost-effectiveness analysis used pooled data from a meta-analysis of the ACT trials.^{16,27} The model classified patients from those trials as follows:

- Responders – ≥50% of treated attacks resulted in pain score of 0 within 15 minutes, without the use of rescue medication.
- Non-responders (partial response) – 1-50% of attacks responded to treatment, as defined above.
- Failure – lack of adherence or efficacy and 0% response rate.

The model took a payer perspective and had a time horizon of one year. Costs were derived from a United States health economy. It was assumed that:

- 20% of patients fail treatment with gammaCore immediately while around a third respond and the remainder have at least a partial response. After assessment and re-training it was assumed that half of the partial responders become responders, and the remainder were non-responders.
- Responders reduced their use of acute treatments by 50% (in line with the definition of response).
- Treatment costs were \$590 per month for gammaCore, while standard care for episodic cluster headache was \$10,056 per year.
- Treatment response was associated with a utility of 0.82; non-response had a utility of 0.72.

The model found that gammaCore plus standard care cost £9,510 and resulted in an estimated 0.83 quality-adjusted life years (base case). Standard care alone cost £10,040 and resulted in 0.74 QALYs. The ICER was -£5,890/QALY, in favour of gammaCore. The model was repeated for 100,000 iterations, and >95% of simulations found gammaCore cost-effective at a cost-effectiveness threshold of \$20,000 per QALY.

Treatment and prophylaxis of chronic cluster headache

A cost-effectiveness analysis used data from the PREVA trial to assess the 1 year cost-effectiveness of gammaCore for acute treatment of chronic cluster headache compared with standard care.²⁸ 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), which may alter the cost-effectiveness of gammaCore in the UK.

Table 4: cost-effectiveness analysis of nVNS for chronic cluster headache

	nVNS + SoC	SoC alone	Difference
Probability of response	0.489	0.083	-
Abortive treatments per 14 days:			
Zolmitriptan (intranasal)	1.6	1.3	-
Sumatriptan (SC)	2.8	7.5	
Oxygen	6.5	10.8	
Cost of gammaCore	€0.87 per dose	-	-
Mean annual cost*	€7,096.96 (£6,318.04)	€7511.35 (£6,686.95)	-€414.39 (£368.91)
QALYs gained per patient	0.607	0.522	+0.085

*UK equivalent costs calculated using exchange rate on 25th July 2018.

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

	Cost used in model	Equivalent in GBP*	Actual UK cost (ex. VAT)
Subcutaneous sumatriptan	€31.31	£27.87	£19.75
Intranasal zolmitriptan	€14.07	£12.53	£6.08
Estimated cost of oxygen per headache treated	€2.87	£2.56	Unable to estimate
gammaCore	€0.87	£0.77	£0.75

*UK equivalent costs calculated using exchange rate on 25th July 2018.

Actual UK costs based on the Drug Tariff, July 2018.

Points to consider

Clinicians in the region highlight that there is a significant unmet need for patients with chronic cluster headache. They propose to use gammaCore in these patients only when verapamil and topiramate have failed, and before trialling lithium or implanted devices or other invasive treatment. There was no appetite to use gammaCore in migraine patients. One consultant felt that use of gammaCore had helped avoid the need for invasive neurostimulation in some patients, and has made a substantial difference in quality of life for patients who respond.²⁹

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 ($\geq 80\%$ 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.^{9,18} Where treatment satisfaction was reported, around 40-45% of patients were satisfied or very satisfied.^{18,19}

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.⁸

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