ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Noninvasive Vagus Nerve Stimulation for Cluster Headache and Migraine

A Health Technology Assessment

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Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Cluster headache and migraine are 2 types of headache disorders. With cluster headache, people experience severe attacks of pain on 1 side of the head. The attacks happen often and in groups or "clusters." Migraines are headaches that happen repeatedly and cause moderate to severe pulsating pain, usually on 1 side of the head. Cluster headache and migraine can cause substantial disability and affect people's quality of life.

Many people with cluster headache or migraine find it difficult to manage their headache pain with standard medications. Others may experience side effects, be unable to take medications, or simply prefer to treat their pain without medications. Noninvasive vagus nerve stimulation (nVNS) is a nondrug, noninvasive treatment option that delivers a mild electrical stimulation to a nerve in the neck. It is intended to reduce the pain of a headache attack, make the attack shorter, or reduce the frequency of the headache attack.

This health technology assessment looked at how safe, effective, and cost-effective nVNS is for the acute treatment and prevention of cluster headache or migraine. It also looked at the budget impact of publicly funding nVNS and at the experiences, preferences, and values of people with cluster headache or migraine.

What Did This Health Technology Assessment Find?

nVNS may be effective and generally safe for the acute treatment and prevention of cluster headache or migraine, but the evidence is uncertain and depends on the specific headache population and indication.

nVNS in addition to standard care could be a cost-effective option for the prevention of cluster headache, but not for the prevention of migraine. Publicly funding nVNS for the prevention of cluster headache would lead to additional costs of $9.92 million over 5 years. Publicly funding nVNS for the acute treatment of migraine would lead to additional costs of and $1.12 billion over 5 years. Publicly funding nVNS for the prevention of migraine would lead to additional costs of $287.77 million over 5 years.

People with cluster headache and migraine described the negative effects of living with their condition. Most reported that medications helped to relieve their headache symptoms; all were interested in trying nVNS as a noninvasive option.

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A Note About Terminology

The literature included in this health technology assessment uses the terms “prevention” and “preventive treatment” equally. We have used these terms interchangeably throughout.

Abstract

Background

Cluster headache and migraine are 2 distinct types of primary headache that can cause substantial pain, disability, and decreased quality of life. Noninvasive vagus nerve stimulation (nVNS) is a treatment option that delivers a mild electrical stimulation to a nerve in the neck. nVNS is intended to reduce the pain and duration of a headache attack, and to prevent headaches from occurring. We conducted a health technology assessment of nVNS for the acute treatment and prevention of cluster headache or migraine, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding nVNS, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Cochrane Risk of Bias tool and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted 2 cost–utility and cost-effectiveness analyses with a 1-year time horizon from a public payer perspective. We also analyzed the budget impact of publicly funding nVNS for people with cluster headache and migraine in Ontario. To contextualize the potential value of nVNS, we spoke with people with cluster headache and migraine.

Results

We included 8 randomized trials in the clinical evidence review (3 on cluster headache, 5 on migraine). For the acute treatment of cluster headache with nVNS, we found no statistically significant improvements in terms of overall response (pain relief), pain freedom, and duration of attacks (GRADEs: Low to Very low), or acute medication use (GRADE: Moderate). We observed little to no difference in mean pain intensity or adverse events (GRADE: Low). For the preventive treatment of cluster headache (based on 1 trial), nVNS reduced the frequency of attacks per week (GRADE: Low), improved response (GRADE: Low), reduced acute medication use (GRADE: Low), and improved quality of life (GRADE: Low to Very low). More overall adverse events were observed with nVNS, but results were uncertain (GRADE: Low). For the acute treatment of migraine (based on 1 study), nVNS improved response to treatment (i.e., pain relief; GRADE: Moderate to Low) but had little to no effect on sustained response (GRADE: Low). nVNS improved pain freedom, but the results were not statistically significant (GRADE: Moderate) and there was no difference in sustained pain freedom (GRADE: Low). There was little to no difference in mean pain intensity (GRADE: Very low) or acute medication use (GRADE: Low), and the risk of adverse events was very uncertain (GRADE: Very low). For the preventive treatment of migraine (based on 4 studies), nVNS may slightly reduce the number of headache and migraine days, but we could not exclude the possibility of no effect (GRADE: Low). nVNS made little to no difference in acute medication use (GRADE: Low), and the evidence was very uncertain for the impact on functional status (GRADE: Very low). nVNS may make little to no difference in adverse events, but the evidence was very uncertain (GRADE: Low to Very low).

For the prevention of cluster headache, nVNS in addition to standard care was more effective and more costly than standard care alone. The incremental cost-effectiveness ratio (ICER) for nVNS in addition to

standard care compared with standard care alone was $27,338 per QALY gained. The probability of nVNS in addition to standard care being cost-effective was 88.5% at a willingness-to-pay (WTP) value of $50,000 per QALY gained and 97% at a WTP value of $100,000 per QALY gained. However, these results need to be interpreted with caution because the clinical inputs used to inform the model were of Low to Very low quality based on the GRADE framework. For the prevention of migraine, nVNS in addition to standard care was similarly effective but more costly than standard care alone. The ICER for nVNS in addition to standard care compared with standard care alone was $952,116 per QALY gained. nVNS was unlikely to be cost-effective at commonly used WTP values of $50,000 and $100,000 per QALY gained. The 5-year budget impact of publicly funding nVNS in Ontario for cluster headache was estimated to be $11.88 million for acute treatment and $9.92 million for preventive treatment. The 5-year budget impact of publicly funding nVNS for migraine was estimated to be $1.12 billion for acute treatment and $278.77 million for preventive treatment.

People with cluster headache and migraine described the negative impact of these conditions on their day-to-day activities, work, social life and family relationships, and mental health. They reflected on their experiences of seeking proper treatment. One participant who had tried nVNS did not see positive effects on their symptoms, but all participants were interested in trying nVNS. Participants emphasized the importance of noninvasive treatment options for cluster headache and migraine.

Conclusions

nVNS may be an effective and generally safe treatment option for people with cluster headache or migraine, but the evidence was of Very low to Moderate certainty, and the degree of effect was dependent on the type of headache and the indication for treatment. nVNS in addition to standard care is likely to be cost-effective for the prevention of cluster headache, but not for the prevention of migraine. We estimate that publicly funding nVNS for the acute treatment of cluster headache in Ontario would result in an additional cost of $11.88 million over 5 years. Publicly funding nVNS for the preventive treatment of cluster headache in Ontario would result in an additional cost of $9.92 million over 5 years. Publicly funding nVNS for migraine would result in very high additional costs: $1.12 billion for acute treatment and $287.77 million for preventive treatment over 5 years. People with cluster headache and migraine were interested in nVNS as a noninvasive option for treatment and prevention.

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Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of noninvasive vagus nerve stimulation for people with cluster headache or migraine. It also evaluates the budget impact of publicly funding noninvasive vagus nerve stimulation and the experiences, preferences, and values of people with cluster headache or migraine.

Background

Health Condition

Cluster Headache

Cluster headache is characterized by severe attacks of pain on 1 side of the head. Pain is most often felt behind or around the eye; other common symptoms include redness or watering of the eye, a stuffed or runny nostril, drooping or swelling of the eyelid, and restlessness or agitation. Cluster headaches are considered among the most painful types of headache – the pain is often described as excruciating, or as a sharp burning or piercing sensation in the head.[1,2]

Cluster headaches develop suddenly, most often without warning. An attack typically lasts from 15 minutes to 3 hours and occurs up to 8 times a day.[1] Most often, attacks occur in clusters that last weeks to months, followed by a pain-free remission period that can last months to years.[1] Cluster headaches are further categorized as episodic or chronic, based on the duration of remission between cluster periods. Most people have episodic cluster headaches with remission periods[3]; those who have headaches for more than 1 year without remission, or with remission periods of less than 3 months, are classified as having chronic cluster headaches.[2]

The exact cause of cluster headaches is not known, but there appears to be a genetic predisposition because cluster headaches have been linked within families.[4] Attacks tend to have periodicity (i.e., they happen at a specific time of day or year), and they may be triggered or worsened by alcohol, histamine, or nitroglycerin.[4]

Migraine

Migraine is a disabling headache disorder characterized by recurrent episodes of pulsating headache. Migraine without aura is the most common type, and is defined by recurrent headaches (at least 5 attacks) lasting from 4 to 72 hours with specific headache characteristics.[2] The most frequent symptoms include unilateral pulsating pain with moderate to severe intensity, aggravation by routine movement or activity, nausea, sensitivity to light, and sensitivity to noise. The other type is migraine with aura; with this type, people experience transient visual, sensory, or other neurological symptoms that typically precede (or sometimes accompany) the headache and can last up to an hour.[2]

Migraine can be further classified as episodic or chronic, based on the number of headache days per month. Chronic migraine is defined as a headache that occurs on 15 or more days per month for more than 3 months, with migraine features on at least 8 days per month.[2] Migraines that occur on fewer than 15 days per month are considered to be episodic.

The exact cause of migraines is not known. Migraines are thought to have a strong genetic basis; most people who experience migraines have a family history of the condition.[5] Among women, migraine often relates to changes in hormones. Other common probable triggers for migraine include stress, an irregular sleep schedule, diet, alcohol, changes in the weather, and certain odours.[5]

Clinical Need and Population of Interest

Cluster Headache

Limited Canadian data are available on cluster headaches. Combined global population-based studies estimate that 0.1% of the population has cluster headaches. The typical age of onset is approximately 30 years, and the condition primarily affects adults.[1] Men are 3 times more likely than women to experience cluster headaches. An estimated 10% to 15% of people with cluster headaches are considered to have chronic cluster headache.[1,3]

Cluster headaches are extremely debilitating, affecting people's quality of life and interfering with their ability to participate in daily activities, social activities, or work.[6] Studies have also found a high prevalence of secondary psychiatric comorbidities, including depression, anxiety, and suicidal thoughts during an attack.[3]

Migraine

In Ontario in 2010/11, 8.8% of the population were estimated to have a diagnosis of migraine.[7] However, this is likely an underestimate, because many of those who experience migraine do not seek medical care and do not have a clinical diagnosis. Based on Canadian data over the same time period, women were more likely to report migraine than men (11.8% vs. 4.7%), with prevalence highest among those aged 30 to 49 years (12.1% overall, 17% for women, and 6.5% for men), and an average age of diagnosis at 26 years.[7] Migraine can also impact adolescents: a Canadian survey reported that 2.4% of youth aged 12 to 14 years and 5% of youth aged 15 to 19 years experience migraine.[8]

Migraine greatly affects people's quality of life; it is considered the second leading cause of disability around the world – first among women and girls aged 15 to 49 years.[9] In Canada, people with migraine reported substantial impacts on sleep, avoidance of activities, limitations in job opportunities, and missed employment days or lost productive time.[7] Mental health comorbidities such as anxiety and depression are also common among people with migraine, reported by an estimated 38.2% of those with chronic migraine and 27% of those with episodic migraine.[10]

Current Treatment Options

Treatment for cluster headache and migraine can be separated into 2 main types: acute (also known as symptomatic or abortive) and preventive (also known as prophylactic). Acute treatment aims to stop the headache pain once it has started, with the goal of reducing the pain as quickly as possible.[11,12] Preventive treatment aims to reduce the frequency, intensity, and duration of attacks, as well as improving response to and minimizing the use of acute medications.[12,13] People with cluster headache may also require transitional preventive medications, which are used at the beginning of a cluster for a short period until the long-acting preventive treatment takes effect.[12]

Selection of an appropriate treatment is individualized and multifactorial, considering a combination of clinical features of headache, level of impairment, comorbidities, contraindications, individual preferences, and cost of treatment.[14]

Cluster Headache

Acute Treatment

The acute treatment of cluster headache is predominantly pharmacological and often requires a combination of medications to be effective. First-line treatment options are triptans (administered subcutaneously or as a nasal spray) and oxygen inhalation therapy, used alone or in combination.[12,15]

Other acute treatment options that are used less often or have lower-quality evidence supporting their use include intranasal lidocaine and octreotide.[15,16] Sphenopalatine ganglion stimulation is an invasive procedure that has been listed as a treatment option by the American Headache Society,[16] but clinical experts have noted that it is not readily available for use in Ontario.

Transitional and Preventive Treatment

Transitional treatment options for cluster headache (to be used temporarily until preventive treatment has reached therapeutic levels) are generally limited to oral corticosteroids or suboccipital steroid injections (occipital nerve blocks).[12,16] Subcutaneous or intramuscular dihydroergotamine is also considered to be a transitional treatment option for some.[12,15]

The specific timing of preventive therapy is highly individualized to a patient's specific cluster history, but it generally continues for 1 or 2 months after the person becomes asymptomatic.[12] People with chronic cluster headaches may need to use prophylaxis indefinitely. The most used preventive treatment option for cluster headache is verapamil, a calcium channel blocker.[12,15,17] However, this medication has considerable potential for adverse effects and cardiac impacts; regular electrocardiogram monitoring is needed during treatment when it is given at higher doses. Lithium is considered a second-line agent for cluster headache prevention, but it often requires blood testing to ensure that an appropriate therapeutic range is achieved; it can also be associated with toxic effects even when levels are within the therapeutic range.[12,17] Other medications that may be effective include warfarin, melatonin, or topiramate.[16,17] However, all of the standard care preventive medications currently being prescribed in Canada for cluster headache are being used off-label.

More recently, the monoclonal antibody galcanezumab has been approved by Health Canada to treat episodic cluster headache for adults who have cluster headache periods that last at least 6 weeks and who have had inadequate response, intolerability, or contraindications to standard care options.[18]

Invasive procedures (e.g., occipital nerve stimulation) and surgical procedures (e.g., deep brain stimulation) exist,[16] but they are reserved for people with the most severe, treatment-refractory symptoms. Clinical experts have noted that these options are not readily accessible or considered to be standard treatment options in Ontario.

Migraine

Acute Treatment

Based on the Canadian Headache Society guideline, the first-line treatment option for acute migraine in adults is pharmacotherapy.[19] Mild to moderate attacks are first treated with oral nonsteroidal anti-inflammatory drugs (NSAIDS; e.g., ibuprofen, acetylsalicylic acid, diclofenac, naproxen) or acetaminophen. People with moderate to severe attacks, or for whom NSAIDs fail, are treated with triptans (e.g., almotriptan, sumatriptan) or a combination strategy (e.g., naproxen and sumatriptan). Antiemetics are also recommended for the treatment of associated nausea or vomiting. Ergots (i.e., nasal or subcutaneous dihydroergotamine) can be used for people who do not respond satisfactorily to other medications, but Ontario experts have noted that they are seldom used, and they have limited availability in the Ontario primary care setting.[19]

Peripheral nerve blockade with the injection of local anesthetic at various nerve branches is also available in Canada and covered in Ontario.[11] This treatment can be used when other acute treatments have been ineffective, or as a form of transition to preventive treatment. A calcitonin gene-related peptide (CGRP) receptor antagonist (ubrogepant) has recently been approved for use in Canada for the acute treatment of migraine in adults.[13]

Acute treatment of migraine in adolescents (aged 12 to 17 years) is similar to that for adults; United States guidelines support the use of ibuprofen, acetaminophen, and oral triptans.[20] However, data are limited with respect to the efficacy of many medications and interventions in this population, so other treatments are often used off-label. No Canadian guidelines are available for the treatment of migraine in adolescents.

Preventive Treatment

People who experience frequent migraine attacks may have substantial disability and reduced quality of life, despite appropriate treatment with acute therapies. Overuse of acute treatment can also lead to more frequent headaches. People with frequent headaches may be considered for preventive treatment.[14] Canadian guidelines (2012) have estimated that preventive treatment is offered to approximately 25% of all adults who experience migraine.[14]

Multiple pharmacological treatments are available for prevention, and decisions about first-line therapy are individualized to the person receiving treatment. Common first-line treatments for adults include beta-blockers (e.g., propranolol, nadolol, metoprolol) and tricyclic antidepressants (e.g., amitriptyline). Other pharmacological options include antiepileptics (e.g., topiramate, gabapentin) or other blood pressure medications (e.g., verapamil, candesartan). Botulinum toxin type A is also approved in Canada for people with chronic migraine.[13,14]

More recently, several CGRP monoclonal antibodies have been developed and approved for use in migraine prevention (i.e., epitinezumab, erenumab, fremanezumab, galcanezumab). However, these treatments are generally reserved for those who have had chronic migraine and an inadequate response to at least 2 oral medications, because they are substantially more expensive than other oral treatments.[13] A CGRP receptor antagonist (atogepant) has recently been approved for use in Canada for the prevention of episodic migraine in adults.[13]

Preventive treatment for adolescents is limited by a lack of evidence. Current American Headache Society guidelines recommend shared decision-making with patients and caregivers[21]; potentially effective pharmacotherapy options for pain relief include propranolol, topiramate, cinnarizine, or amitriptyline with cognitive behavioural therapy.

In addition to pharmacotherapy, lifestyle factors (e.g., appropriate sleep, eating regular meals, reduced stress, regular exercise) and trigger management (factors that might increase probability of a migraine) are important for the prevention of migraine headaches for both adults and adolescents.[14,21]

Limitations of Current Treatment Options

Despite the availability of acute and preventive treatment regimens, treatment for both types of headache disorders is often complex, with people experiencing incomplete effect, substantial adverse effects, contraindications, or suboptimal uptake or adherence to treatment.[22] Many treatments also require frequent monitoring of blood or vital signs (e.g., verapamil, lithium) or visits to the physician or hospital for injections (e.g., nerve blocks, botulinum toxin type A), and some are not easily portable outside of home (e.g., oxygen therapy for cluster headache).[15] As well, clinical guidelines for the acute treatment of cluster headache and prevention of both cluster headache and migraine are often based on treatments that are not approved for use in these conditions. As a result, an individualized process of trial and error is often required to determine an optimal treatment strategy.[14-16,21]

The cost of treatment is often a prohibitive factor for many available medications because public drug coverage is not available for most people over age 25 years or under age 65 years in Ontario, and many of the pharmacotherapies recommended are not publicly funded. Similarly, oxygen therapy is not funded for cluster headaches in Ontario.

Last, many people are pharmacotherapy-averse or want to avoid injectable treatments. In particular, many adolescents and women of child-bearing age wish to avoid or minimize the use of pharmacotherapy, which can have substantial side effects.[20,21] As well, safety and effectiveness data for pharmacological treatment are often limited to adults. Nondrug, noninvasive options may be more favourable for these populations.[23]

Health Technology Under Review

The vagus nerve is the longest cranial nerve in the body; it runs from the lower part of the brain through the neck to the chest, stomach, and large colon.[24] Noninvasive vagus nerve stimulation (nVNS) involves using a device to stimulate the vagus nerve transcutaneously (i.e., through direct contact with the skin) with electrical impulses. Although the mechanism of action is not fully understood, stimulation of the vagus nerve is thought to send electrical impulses to the brain, blocking pain signals to prevent or relieve headache pain.[24]

At the time of writing, only 1 nVNS device is available and approved for headache use in Ontario. The device is a small, handheld, patient- or carer-controlled device that delivers gentle electric stimulation to the vagus nerve via the neck.[25] The person holds the device directly to their neck and can control the level of intensity based on their comfort level. For acute treatment, the device is applied at the earliest sign of pain, with 2 stimulations lasting 2 minutes each on the same side of the neck; this can be repeated as needed while the pain persists, but the device is designed to deliver a maximum of 30 stimulations over 24 hours. For prevention, the device is used twice a day (morning and night) for

2 stimulations lasting 2 minutes each on the same side of the neck. The device uses a refill card to load it with an appropriate number of days of therapy and will stop working until a new refill card is loaded.

The device is contraindicated for people with active implantable medical devices (e.g., hearing aid implants, pacemakers), as well as for people who are using another stimulation device at the same time, or any portable electronic device.[25] According to the manufacturer, common side effects (among less than 2% of people) are listed as site redness; irritation or discomfort; local pain; muscle twitching or contractions in the face, neck, or head area; headache; dizziness; or tingling and prickling. The manufacturer notes that side effects generally resolve when a stimulation is completed, but the long-term effects are unknown.

Other noninvasive stimulation devices have been developed that stimulate the vagus nerve at alternative locations, such as auricular vagus nerve stimulators. However, they are applied differently with different voltages, and minimal information is available about the appropriate use and indications for these devices; they also lack Canadian or US regulatory approvals for headache. As such, these developing devices are beyond the scope of the present review.

Regulatory Information

Only the gammaCore noninvasive vagus nerve stimulator is approved by Health Canada as a Class II device (license No. 89472).[26] The device is approved for the acute treatment and prevention of cluster headache in adults, as well as for the acute treatment and prevention of migraine headache in adolescents (age 12 years and older) and adults.[25]

The gammaCore device is approved for the treatment and prevention of cluster headache and migraine by the US Food and Drug Administration (FDA); however, it is limited to adjunctive use for the prevention of cluster headache, and it specifies only acute treatment for episodic cluster headache.[27] The FDA has also approved the device for the treatment of hemicrania continua and paroxysmal hemicrania. In the European Union, gammaCore is has a CE mark for the acute treatment and prevention of primary headache.[28]

No other nVNS devices have been approved by Health Canada or the US FDA for the acute treatment or prevention of cluster headache or migraine.

Ontario, Canadian, and International Context

Canada and Ontario

The gammaCore device is available in Canada, but it is not publicly funded in Ontario or any other province. Patients can obtain the device through out-of-pocket payment or through private insurance plans. Access to the device requires authorization from a health care provider, which is then submitted directly to the manufacturer (electroCore). Currently, the device costs $650 (plus tax) for a 93-day kit, and 93-day refills cost an additional $650.[29] According to the manufacturer, the device and charging case are supplied at no cost for the first course of therapy; the fee includes the cost of a course of therapy. For long-term users of the device, a 36-month kit is also available, which costs $6,500.

According to the manufacturer and clinical experts, current uptake of the device in Ontario is low, but it is being prescribed for both cluster headache and migraine.

International

In England and Scotland, gammaCore is being used and reimbursed for the treatment of cluster headache based on evidence from a technology assessment and guidance from the National Institute for Health and Care Excellence (NICE) in 2019.[30,31] Reimbursement is based on a free 3-month trial of the device, and on a recommendation that the device be discontinued for people whose symptoms do not decrease in the first 3 months of treatment. The device is not reimbursed for migraine and has not been evaluated by NICE for this indication.

Other countries have approved and are using gammaCore (e.g., the United States and Australia), but it is not currently funded by most insurers. According to the manufacturer, the device is funded in the US through the Department of Veterans Affairs and in military treatment facilities.[32] However, a review by United Health stated that the device was not considered medically necessary,[33] and a review by Aetna noted that it was investigational.[34] A recent American Headache Society guideline[35] states that neuromodulation, including nVNS, may be offered to all people with migraine and may be appropriate for acute treatment among those with contraindications, poor tolerability, or inadequate response to standard care (used alone or in combination with pharmacotherapy). The American Headache Society also notes that nVNS may be appropriate as an adjunct for the prevention of migraine for people with inadequate response to treatment, frequent attacks, or secondary medication-overuse headache, or as monotherapy for people who prefer to avoid medication or who have poor tolerability or contraindications to triptans.[35]

Equity Context

We use the PROGRESS-Plus framework[36] to help explicitly consider health equity in our health technology assessments. PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence; race or ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes.

Biological differences have been observed in patient populations: more women experience migraine than men, and more men have cluster headache than women. As well, disparities in migraine prevalence, disability, and access to treatment have been identified among marginalized and underserved groups.[37] However, we did not identify any specific PROGRESS-Plus subgroup or population that would likely benefit more from nVNS over another.

If nVNS is found to be effective, public funding may improve access to an effective treatment for people who cannot afford the treatment out of pocket or who do not have private insurance coverage. As well, funding this technology could reduce inequity because of improved access to therapy for people in remote areas who require treatment at the physician's office (e.g., nerve block injections, botulinum toxin type A injections), or who require regular drug monitoring. Patients may prefer the nVNS device because it is handheld, operated by the patient, and can be used both at home and away from home more easily than other commonly used treatments (e.g., oxygen treatment).

Expert Consultation

We engaged with experts in the specialty areas of neurology and headache to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42023466355), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Questions

- What are the effectiveness and safety of noninvasive vagus nerve stimulation (nVNS) for the acute treatment or prevention of cluster headache in adults?
- What are the effectiveness and safety of nVNS for the acute treatment or prevention of migraine in adults and adolescents?

Methods

Clinical Literature Search

We performed a clinical literature search on September 13, 2023, to retrieve studies published from inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[38]

We created database auto-alerts in MEDLINE and Embase and monitored them until March 1, 2024. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Randomized controlled trials (RCTs), nonrandomized controlled trials, and comparative nonrandomized studies (i.e., studies with a minimum of 2 study arms)
- Systematic reviews (including health technology assessments with a systematic review) that matched our research question and inclusion criteria (systematic reviews had to clearly report literature search methods, including [at a minimum] information about the databases searched [at least 2], search terms, and search dates)

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, editorials, commentaries, case reports, case series, conferences abstracts, letters

Note: We assessed whether it was appropriate to leverage any eligible systematic reviews identified through the literature search, based on factors such as recency, quality, and other limitations (e.g., methodological rigour, internal validity, relevance). Systematic reviews that answered only a portion of the research question, combined multiple populations in meta-analysis, excluded non-RCTs, or did not report on all relevant study outcomes were excluded from analysis and used as a reference source for primary studies.

Participants

- Cluster headache: adults (aged 18 years and older) with cluster headache
- Migraine: adults (aged 18 years and older) or adolescents (12 to 17 years) with migraine

Interventions

Inclusion Criteria

- nVNS applied at the neck for the acute treatment or prevention of headache (alone or in addition to standard care)

Exclusion Criteria

- nVNS applied at the ear (i.e., auricular branch)

Comparators

Inclusion Criteria

- Standard care (as defined by the study), with or without sham
- No treatment, with or without sham

Exclusion Criteria

- Other invasive or noninvasive neuromodulation devices (e.g., external trigeminal nerve stimulation) or comparing different applications of the devices

Outcome Measures

- Headache pain (pain outcome measures were as defined by individual studies)
  - Pain relief (e.g., response, pain relief at defined time, sustained pain relief at defined time, time to pain relief)
  - Pain freedom (e.g., pain free at defined time, sustained pain freedom at defined time, time to pain freedom)
  - Headache intensity (severity of headache pain)
- Frequency of headache attack (e.g., response, days with headache or migraine, attacks per week; as defined by individual studies)
- Duration of headache attack
- Acute medication use (change in dosage and/or frequency)
- Patient-reported disability and functioning (e.g., results from the Migraine Disability Assessment Test, Headache Impact Test)
- Adverse events
- Quality of life
- Patient preferences and satisfaction
- Health care resource use

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. A single reviewer then screened all remaining citations using Covidence[39] and obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

Equity Considerations

Potential equity issues related to the research question were not evident during scoping. However, we report the available characteristics of participants in included studies (e.g., PROGRESS-PLUS characteristics).

Statistical Analysis

When possible and when clinical heterogeneity was considered low, we undertook a meta-analysis of individual studies using Cochrane RevMan.[40] Studies were pooled using a Mantel–Haenszel random-effects model for dichotomous outcomes (calculated using relative risks with 95% confidence intervals [CIs]) and an inverse variance random-effects model for continuous outcomes (calculated using mean differences with 95% CIs).

We provided a narrative summary of the results when meta-analysis was not appropriate. The preferred measures of effect for categorical outcomes were risk difference, risk ratio, and odds ratio. The measures of effect for continuous outcomes were mean difference and the median difference.

When data from multiple analyses were available, preference was given to those that used an intention-to-treat analysis over per-protocol or modified intention-to-treat analyses. When multiple measures were reported for a continuous outcome, preference was given to those that reported absolute mean changes in scores over percent reductions, to enhance transparency of data. Outcomes that were reported at the level of the participant (i.e., means or proportions per person) were preferred; outcomes reported at the level of attacks (i.e., denominator of total number of attacks) have been included in an appendix.

All relevant study outcomes were extracted, but our analysis and critical appraisal were focused on the most clinically relevant outcomes as defined by the International Headache Society guidelines (e.g., migraine pain relief and pain freedom at 120 minutes).[41-45] All results are reported separately by type of treatment indication: acute treatment or prevention, where possible.

Subgroup Analyses

We performed planned subgroup analyses for episodic versus chronic headaches, where data permitted. Subgroup analysis was planned based on treatment failure (i.e., people who failed prior treatment vs. new or ongoing treatment), but insufficient data were available to perform the analysis.

Critical Appraisal of Evidence

We assessed risk of bias using the Cochrane Risk of Bias tool for RCTs[46-48] (Appendix 2).

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[49] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The database search of the clinical literature yielded 385 citations, including grey literature searches and after duplicates were removed, published from database inception to September 13, 2023. We identified no additional eligible studies from other sources, including database alerts (monitored until March 1, 2024). In total, we identified 11 studies (7 RCTs reported in 11 publications) that met our inclusion criteria. See Appendix 3 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the clinical literature search.

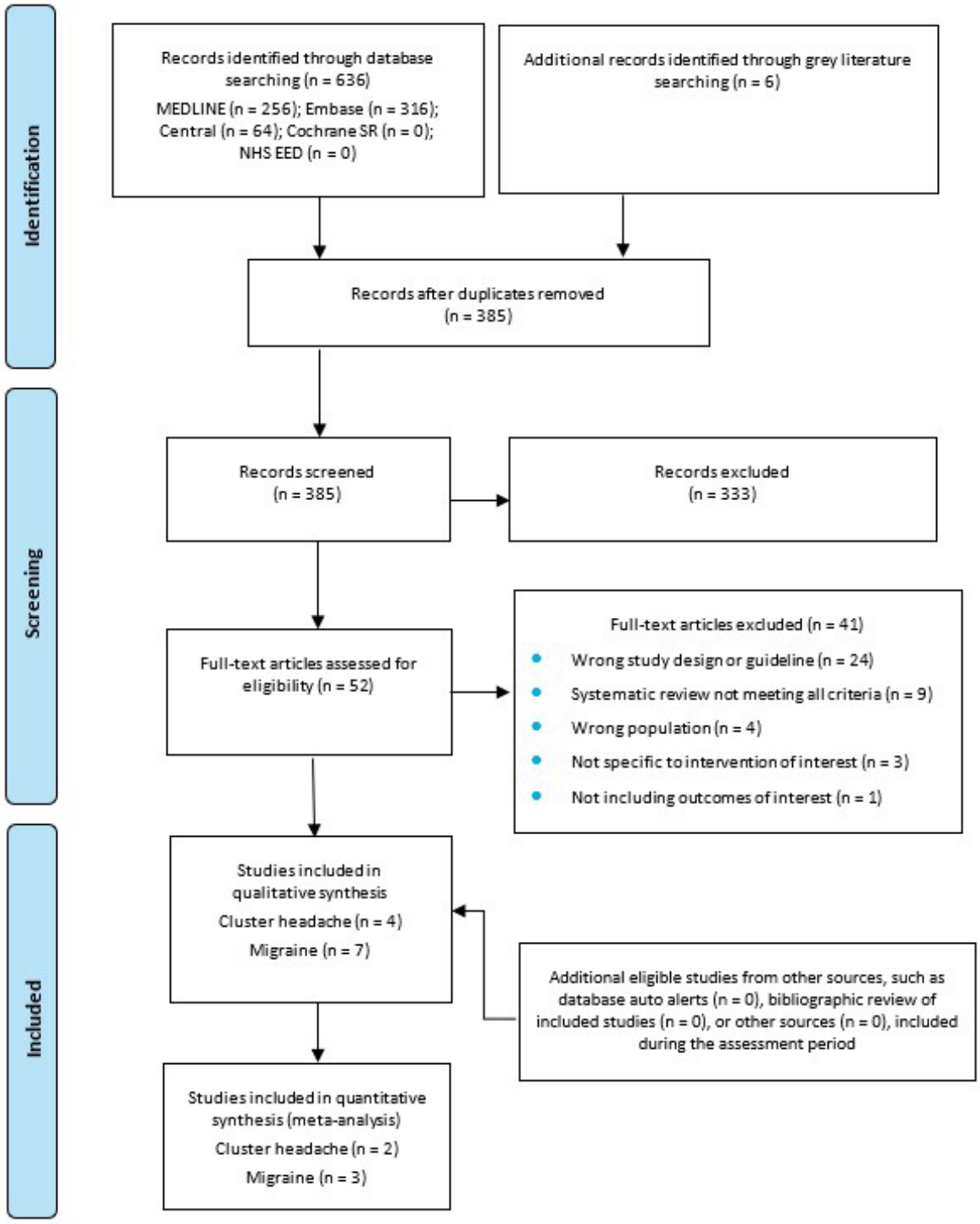

Figure 1: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The clinical literature search yielded 385 citations, including grey literature results and after removing duplicates, published between database inception and September 13, 2023. We screened the abstracts of the 385 identified studies and excluded 333. We assessed the full text of 52 articles and excluded a further 41. In the end, we included 11 articles in the qualitative synthesis and 5 in the quantitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[50]

Of the included studies, 3 (reported in 4 publications)[51-54] evaluated the use of the device for people with cluster headache and 5 (reported in 7 publications)[55-59] evaluated the use of the device for people with migraine.

We identified 9 systematic reviews or health technology assessments that met the general inclusion criteria for the present review, but we excluded them because they were outdated, included only a subset of the research question (e.g., only acute treatment, only prevention, only populations with episodic headache, only populations with chronic headache), combined results from multiple populations or interventions, were of very low quality, or excluded studies. We also excluded network meta-analyses from the present review. We also identified 1 pooled analysis of 2 RCTs that are included in the present review, but we excluded the pooled analysis because it was neither a systematic review nor a primary study.[60] A list of selected excluded studies is provided in Appendix 3.

Cluster Headache

Characteristics of Included Studies

The characteristics of the included studies on cluster headache are summarized in Table 1.

Three RCTs (published in 4 studies) evaluated the use of the gammaCore nVNS device in addition to standard of care for cluster headache. Two RCTs (the ACT1[51] and ACT2 trials[52]) evaluated the use of the device for the acute treatment of cluster headache and 1 RCT (the PREVA trial[53,54]) evaluated the use of the device for the preventive treatment of cluster headache. The PREVA trial also allowed participants the option of treating their acute headaches with the nVNS device, but this was not standardized or clearly reported, so we evaluated relevant outcomes for prevention only.

Two studies were performed in Europe,[52,53] and 1 study was performed in the United States.[51] For the 2 studies evaluating the acute use of nVNS, the protocols differed: both studies allowed for 3 consecutive doses at the time of an attack, but 1 study specified application to the right side of the neck[51] and the other specified application ipsilateral to the side of pain.[52] As well, 1 study[52] allowed an additional 3 doses if the pain was not aborted within 9 minutes (with a minimum of 6 hours between sessions), but the other[51] did not allow for additional doses and required a minimum of 12 hours between sessions.

The 2 studies that evaluated nVNS for the acute treatment of cluster headache included people with both episodic and chronic cluster headache, subgrouping by each.[51,52] The 1 study that evaluated nVNS for the prevention of cluster headache included only people with chronic cluster headache.[53]

The 2 studies that evaluated nVNS for the acute treatment of cluster headache compared nVNS with standard of care plus a sham device[51,52]; the prevention study was an open-label design that compared nVNS with standard of care alone.[53] All included studies reported follow-up data for the randomized, controlled period, as well as for an open-label period in which people in the control group (standard of care) switched to nVNS for the remainder of the study. Given that an open-label period is not a true cross-over design and no longer includes a control group, we have reported only data from the randomized, controlled periods, apart from device-related adverse events.

All studies applied a large number of exclusion criteria, which are summarized in Appendix 4.

Table 1: Characteristics of Studies Included in the Clinical Literature Review, Cluster Headache

Author, year (study)	Country, sites, n	Sample size, n	Population	nVNS indication and protocol	Intervention	Comparator	Length of follow-up[a]
Gaul et al, 2016[53] (PREVA) *Gaul et al, 2017[54] (PREVA post hoc)*	Europe (4 countries), 10	97	Adults (18–70 y) Chronic cluster headache (ICHD 3B)	Prevention: 3 doses, 5 min apart, 2 times/d, right side of neck Acute treatment: optional, 3 doses at pain onset[b]	nVNS and standard of care	Standard of care	4 wk
Silberstein et al, 2016[51] (ACT1)	United States, 20	150	Adults (18–75 y) Episodic or chronic cluster headache (ICHD 2)	Acute treatment: 3 doses to right side of neck; only 1 attack treated per 12 h	nVNS and standard of care	Sham and standard of care	1 mo or until 5 cluster headache attacks were treated
Goadsby et al, 2018[52] (ACT2)	Europe (4 countries), 9	102	Adults (≥ 18 y) Episodic or chronic cluster headache (ICHD 2)	Acute treatment: 3 doses ipsilateral to attack; if not aborted in 9 min, 3 additional doses. Minium 6 h between sessions	nVNS and standard of care	Sham and standard of care	2 wk

Abbreviations: ICHD, International Classification of Headache Disorders; nVNS, noninvasive vagus nerve stimulation.

[a] Only follow-up during the randomization period was included.

[b] Participants were advised not to administer preventive treatment within 2 h after acute treatment.

A summary of baseline study characteristics is provided in Table 2. Across the 2 acute treatment trials (ACT1[51] and ACT2[52]), the cluster headache populations varied greatly: 1 study included 33% of people with chronic cluster headache[51]; the other, 71%.[52] Participants were predominantly male with a mean age range of 44 to 49 years, and most were classified by study authors as White. The acute medications used most at baseline were triptans and oxygen treatment, and 64% to 68% of participants used some form of preventive medication. The use of preventive medication in the ACT1[51] trial appeared unbalanced between treatment arms: use was higher in the control arm than in the nVNS arm (78% vs. 58%, respectively), and the duration of the last cluster headache attack was higher in the nVNS arm (86 minutes vs. 64 minutes), although no statistical comparisons between groups were performed.

The prevention study by Gaul et al[53] included only those with chronic cluster headache; participants had a mean age of 44 years and were predominantly male (69%). Nearly all used pharmacologic or oxygen treatment for acute attacks; verapamil was used most (by over half of participants) for the prevention of cluster headaches, followed by lithium and topiramate.

Table 2: Baseline Patient Characteristics of Studies Included in the Clinical Literature Review, Cluster Headache

Author, year (study)	Chronic cluster headache, %	Mean age (SD), y	Male, %	Race or ethnicity, %	Mean attack duration (SD), min	Mean no. of attacks in 4 wk (SD)	Preventive medication use, %		Acute medication use, %	
							nVNS	Control	nVNS	Control
Gaul et al, 2016[53] (PREVA)	100	*nVNS* 45.4 (11.0) *Control* 42.3 (11.0)	69.1	NR	*nVNS*[a] 27.4 (19.8) *Control*[a] 29.3 (29.9)	*nVNS* 67.3 (43.6) *Control* 73.9 (115.8)	Verapamil: 52 Lithium: 13 Topiramate: 15 Corticosteroid: 4	Verapamil: 53 Lithium: 18 Topiramate: 14 Corticosteroid: 4	Pharmacologic: 90 Oxygen: 67	Pharmacologic: 90 Oxygen: 69
Silberstein et al, 2016[51] (ACT1)	32.7	*nVNS* 47.1 (13.5) *Control* 48.6 (11.7)	84	*nVNS* Asian: 5.5 Black: 6.9 White: 86.3 Missing: 1.4 *Control* Asian: 1.3 Black: 9.1 White: 88.3 Missing: 1.3	*nVNS* 86 (119) *Control* 64 (71)	NR	Overall: 57.5 Verapamil: 15.1 Lithium: 4.1 Topiramate: 2.7 Corticosteroid: 15.1	Overall: 77.9 Verapamil: 26 Lithium: 3.9 Topiramate: 9.1 Corticosteroid: 10.4	Triptan: 57.5 Oxygen: 42.5 Mild analgesic: 17.8 Narcotic: 5.5 Other: 28.8 None: 5.5	Triptan: 70.1 Oxygen: 37.7 Mild analgesic: 20.8 Narcotic: 5.2 Other: 36.4 None: 2.6
Goadsby et al, 2018[52] (ACT2)	70.6	*nVNS* 43.9 (10.6) *Control* 46.9 (10.6)	71.6	*nVNS* White: 98 Asian: 2 *Control* White: 100	*nVNS* 69.9 (68.7) *Control* 77.4 (76.1)	*nVNS* 10 (range, 1–53) *Control* 11 (range 2–39)	1 or more: 64 Verapamil: 36 Lithium: 8 Corticosteroid: 2 Propranolol: 2 Tricyclic: 4 SRA: 4 Antiepileptic: 20	1 or more: 63.4 Verapamil : 44.2 Lithium: 7.7 Corticosteroid: 3.8 Propranolol: 0 Tricyclic: 1.9 SRA: 3.8 Antiepileptic: 11.5	Triptan: 74 Oxygen: 54 Mild analgesic: 14 Narcotic: 6 Other: 10 None: 0	Triptan: 65.3 Oxygen: 59.6 Mild analgesic: 11.5 Narcotic: 0 Other: 15.4 None: 9.6

Abbreviations: NR, not reported; nVNS, noninvasive vagus nerve stimulation; SD, standard deviation; SRA, serotonin receptor antagonist.

[a] With acute pharmacologic medications or oxygen treatment.

Risk of Bias in the Included Studies

The detailed results of the risk of bias assessment are included in Appendix 2.

Overall, the 2 studies that evaluated the acute treatment of nVNS[51,52] were at low to moderate risk of bias, depending on the specific outcome evaluated. Potential issues were noted relating to lack of blinding of training personnel, incomplete outcome assessment, and selective outcome reporting. Analyses based on within-study subgroups (e.g., episodic and chronic cluster headaches) were considered to be at high risk of bias because the studies were not randomized – or powered – to evaluate these subgroups.

The single study that evaluated the preventive use of nVNS[53] was at high risk of bias primarily because of its open-label design and lack of reporting on randomization and concealment, as well as potential issues related to selective outcome reporting and incomplete outcome data. The lack of blinding and use of a sham control were concerning, given that all outcomes were reported subjectively based on patient self-report using daily diaries. Although the potential placebo effect with cluster headache trials is considered lower than that for other types of headache, the use of a placebo control is recommended for studies of efficacy.[45]

All analyses based on clearly stated post hoc analyses were considered to have very serious risk of bias.

Acute Treatment – Cluster Headache

Two studies were included in the analysis of the acute treatment of cluster headache with nVNS relative to a sham device and standard of care.[51,52] Results are summarized for each outcome for the overall cohort analysis; available data from study subgroup analyses related to episodic and chronic cluster headache have been presented separately.

Pain

The 2 RCTs (ACT1[51] and ACT2[52]) that evaluated the acute use of nVNS for cluster headache both measured headache pain using a 5-point scale, from 0 (no pain) to 4 (very severe pain). The studies used multiple primary, secondary, and post hoc measures of pain effect (i.e., responder status, pain-free status, intensity of pain, and duration of attack), with different definitions, to assess each outcome.

Pain Relief: Response

The ACT1[51] trial defined a responder as having recorded a pain intensity score of 0 or 1 at 15 minutes. The use of rescue medications within 60 minutes of treatment was considered a treatment failure. The ACT2[52] trial also defined response as a pain intensity score of 0 or 1, but measurements were made at 30 minutes, and any rescue medication use after treatment initiation was considered a treatment failure. The studies also differed in their reported summary measure of effect: ACT1 reported only the proportion of people who achieved response after the first cluster headache attack, whereas ACT2 reported the mean proportion of all attacks per person who achieved response. As such, data could not undergo meta-analysis and have been reported narratively.

Results for the proportion of participants who achieved a response within 15 or 30 minutes of treatment are summarized in Table 3. Overall, both studies found an increase in the proportion of people who achieved response with nVNS versus controls: one observed a 77% relative increase in response for the first treated cluster headache, and the other observed a 15% absolute increase in the mean proportion of

attacks per person who achieved response. However, results were not statistically significant, and confidence intervals included both a reduction in effect and a large response (Table 3). The GRADE level for this body of evidence was Low, downgraded due to risk of bias and imprecision.

Table 3: Response Within 15 or 30 Minutes, nVNS vs. Control, Acute Treatment, Cluster Headache

Author, year (study)	Effect measure	Response definition, pain score; time	Participants, nVNS/ control, n	Responders, %		Summary estimate	*P*
				nVNS	Control		
Silberstein et al, 2016[51] (ACT1)	Proportion who achieved response after first attack	0 or 1; 15 min	60/73	26.7	15.1	RR 1.77 (0.89–3.52)[a]	.1[a]
Goadsby et al, 2018[52] (ACT2)	Mean proportion of treated attacks per person who achieved response	0 or 1; 30 min	48/44	42.7	27.6	Absolute difference: 15.1% (SE 7.3)	.05[b]

Abbreviations: nVNS, noninvasive vagus nerve stimulation; SE, standard error; RR, relative risk.
[a] Calculated in Cochrane RevMan[40] using data provided.
[b] Adjusted for study site.

Pain Relief: Response in 50% or More of Attacks

In post hoc analyses, both the ACT1[51] and ACT2[52] studies evaluated the proportion of people who achieved response (pain score of 0 or 1) at 15 minutes in 50% or more of cluster headache attacks. A meta-analysis of results is presented in Figure 2.

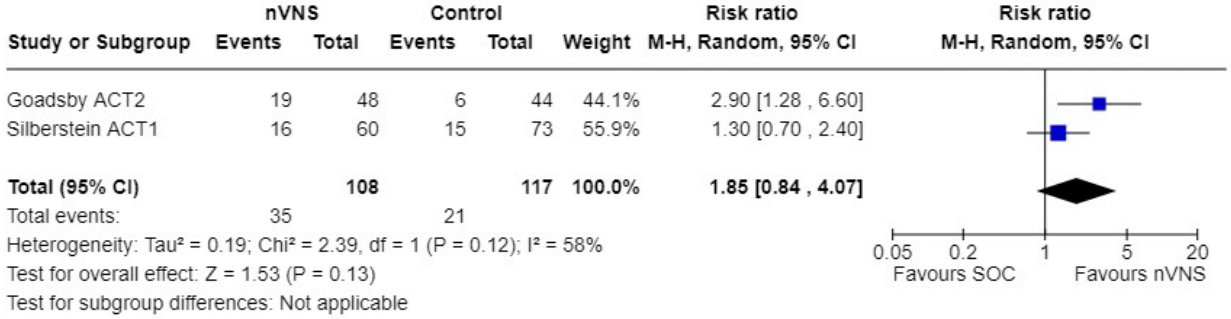

Figure 2: Meta-Analysis of the Proportion of People Who Achieved Response at 15 Minutes in ≥ 50% of Attacks, nVNS vs. Control, Acute Treatment, Cluster Headache

Meta-analysis of the results of 2 studies showed a risk ratio of 1.85 (95% CI 0.84–4.07) for response at 15 minutes in ≥ 50% of attacks with nVNS relative to standard of care.
Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; nVNS, noninvasive vagus nerve stimulation; SOC, standard of care.

Overall, nVNS led to a large increase in response relative to controls; however, results were not statistically significant and confidence intervals spanned both a very large benefit and a reduction in response (relative risk 1.85, 95% CI 0.84–4.07). The GRADE for this body of evidence was Very low, downgraded due to risk of bias and imprecision.

Pain Relief: Sustained Treatment Response

The ACT1[51] trial assessed sustained treatment response, defined as having a pain score of 0 or 1 without the use of rescue medication at 15 to 60 minutes after treatment initiation for the first treated cluster headache attack. Results are shown in Table 4.

Table 4: Proportion of People With Sustained Treatment Response After First Attack, nVNS vs. Control, Acute Treatment, Cluster Headache

Author, year (study)	Participants, nVNS/control, n	Sustained treatment response, %[a]		RR (95% CI)[b]	*P*
		nVNS	Control		
Silberstein et al, 2016[51] (ACT1)	60/73	26.7	12.3	2.16 (1.03–4.54)	.04

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; RR, relative risk.

[a] Pain score of 0 or 1 without rescue medication use at 15 to 60 minutes after treatment initiation for the first treated cluster headache attack.

[b] Calculated from data provided in the publication.

Compared to the outcome of response at 15 minutes (Table 3, above), the same proportion of people using nVNS had a sustained treatment response (26.7%), with a small reduction (2 participants) in the proportion of the control group that achieved sustained treatment response (12.3%, from 15.1% at 15 minutes). Overall, the proportion of people with a sustained treatment response was over 2 times greater with nVNS relative to controls. However, results were uncertain, with confidence estimates ranging from a very small relative increase of 3% to a very large increase. The GRADE for this body of evidence was Low, downgraded due to very serious imprecision.

Pain Freedom

The ACT2 trial[52] evaluated the proportion of treated attacks per person who achieved pain-free status (pain score of 0) at 30 minutes (Table 5). Overall, an average of 7.8 more treated attacks per person achieved pain-free status with nVNS relative to control, but these results did not reach statistical significance. The GRADE for this body of evidence was Low, downgraded due to risk of bias and imprecision.

Table 5: Mean Proportion of Treated Attacks Per Person That Achieved Pain-Free Status at 30 Minutes, nVNS vs. Control, Acute Treatment, Cluster Headache

Author, year (study)	Participants, nVNS/control, n	Mean proportion of treated attacks per person that achieved pain-free status, %		Absolute difference, % (SE)	*P*
		nVNS	Control		
Goadsby et al, 2018[52] (ACT2)	48/44	26.1	18.3	7.8 (6.4)	.17

Abbreviations: nVNS, noninvasive vagus nerve stimulation; SE, standard error.

The ACT2 trial[52] further evaluated the proportion of all treated attacks that achieved pain-free status at 15 minutes relative to controls. Although this was the primary outcome of the study, estimates were not at the level of the individual patient but rather the total number of attacks observed in the study. Findings are summarized in Appendix 5, Table A8.

Pain Freedom in 50% or More of Attacks

As post hoc or exploratory analyses, both the ACT2[52] and ACT1[51] trials evaluated the proportion of people who achieved pain-free status at 15 minutes in 50% or more of attacks. The results of the meta-analysis are shown in Figure 3.

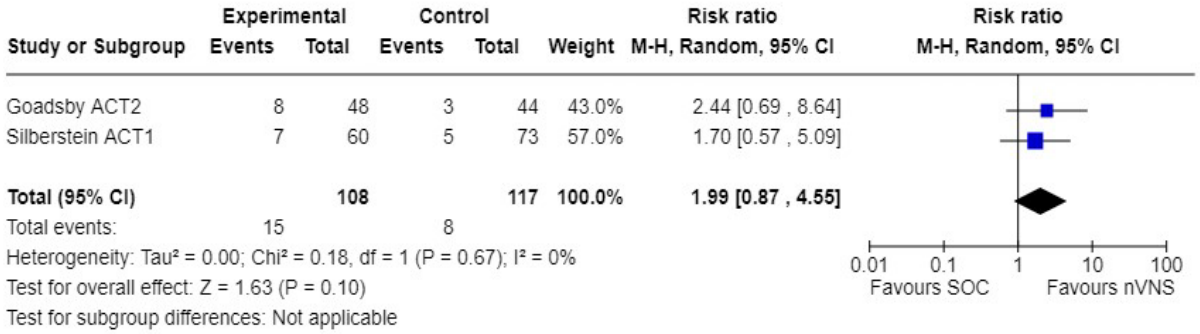

Figure 3: Meta-Analysis of the Proportion of People Who Achieved Pain Freedom at 15 Minutes in ≥ 50% of Attacks, nVNS vs. Control, Acute Treatment, Cluster Headache

Meta-analysis of the results of 2 studies showed a risk ratio of 1.99 (95% CI 0.87–4.55) for pain freedom at 15 minutes in 50% or more of attacks with nVNS relative to standard of care.

Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; nVNS, noninvasive vagus nerve stimulation; SOC, standard of care.

Overall, there was a nearly 2-fold relative increase in the consistency of pain freedom with nVNS relative to controls; however, results were highly imprecise, with confidence intervals including both a decrease and a very large increase in effect. The GRADE for this body of evidence was Very low, downgraded due to risk of bias and imprecision.

Headache Intensity

The mean intensity of pain for treated attacks was reported in both the ACT1[51] and ACT2[52] trials; findings are summarized in Table 6. The ACT1[52] trial evaluated the average of all participants' mean pain intensities at 15 minutes after treatment initiation for all attacks, up to a maximum of 5 attacks per person. The ACT2[52] trial measured the mean change in pain intensity from attack onset to the 15- or 30-minute mark; it included only participants who had treated attacks without the use of rescue medication and for whom data were available on pain at onset and follow-up.

In both studies, reductions in pain intensity were clinically small between nVNS and controls at 15 minutes, with a mean reduction in pain scores of 0.1 points at follow-up in ACT1[51] and a change from attack onset to baseline of 0.4 points in ACT2.[52] The results did not achieve statistical significance for any measure or time point. The GRADE for this body of evidence was Low, downgraded due to risk of bias and imprecision.

Table 6: Pain Intensity, nVNS vs. Control, Acute Treatment, Cluster Headache

Author, year (study)	Effect measure	Minutes after treatment	Participants, nVNS/ control, n	Mean pain intensity (variance)		Mean difference (95% CI)[a]	*P*[a]
				nVNS	Control		
Silberstein et al, 2016[51] (ACT1)	Mean pain intensity for all treated attacks, per person[b]	15	73/60	2.1 (95% CI 1.9 to 2.3)	2.0 (95% CI 1.8 to 2.2)	0.10 (−0.18 to 0.38)	.48
Goadsby et al, 2018[52] (ACT2)	Mean change in pain intensity from attack onset to follow-up measurement, per person[b]	15	36/31	−1.3 (SE 0.2)	−0.9 (SE 0.1)	−0.40 (−0.84 to 0.04)	.07
		30	36/31	−1.6 (SE 0.2)	−1.2 (SE 0.2)	−0.40 (−0.95 to 0.15)	.16

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; SE, standard error.
[a] Calculated from data provided in study.
[b] Measured on a scale from 0 to 4 (0 = no pain; 4 = very severe pain).

Pain: Subgroup Analyses

A summary of results for all pain outcomes for the subgroups of episodic and chronic cluster headache are presented in Tables 7 and 8, below. Each of the analyses are from within-study subgroups and were not powered for subgroup analysis. Given the uncertainty in the subgroup estimates, we have reported all data from each exploratory analysis, but have not subjected them to GRADE assessment.

Overall, we found a trend toward large improvements in pain-related outcomes among those who had episodic cluster headache. However, analyses were not powered for these subgroups, and confidence intervals surrounding estimates were large, indicating substantial imprecision.

In contrast, we observed no statistically significant improvements in pain outcomes among those with chronic cluster headache. Results between studies were often inconsistent, suggesting either an improvement or reduction in effect, and confidence intervals were very large across most estimates.

Table 7: Summary of Subgroup Analyses for Pain-Related Outcomes, nVNS vs. Control, Acute Treatment, Episodic Cluster Headache

Pain outcome	Author, year (study)	Measurement, time	Participants, nVNS/control, n	Mean or proportion		Summary effect (95% CI or SE)	*P*[a]
				nVNS	Control		
Response	Silberstein et al, 2016[51] (ACT1)	Proportion after first attack, 15 min	38/47	34.2	10.6	RR 3.22 (1.26 to 8.22)[b]	.01[b]
	Goadsby et al, 2018[52] (ACT 2)	Mean proportion of treated attacks per person, 30 min	14/13	57.5	25.5	Absolute difference: 32 (15)	.07
Response in ≥ 50% of attacks	Silberstein et al, 2016[51] (ACT1)	Proportion, 15 min	38/47	34.2	14.9	RR 2.30 (1.02 to 5.18)[b]	.05[b]
	Goadsby et al, 2018[52] (ACT 2)	Proportion, 15 min	14/13	64.3	15.4	RR 4.18 (1.10 to 15.85)[b]	.04[b]
Sustained response	Silberstein et al, 2016[51] (ACT1)	Proportion, 15 min sustained to 60 min	38/47	34.2	10.6	RR 3.22 (1.26 to 8.22)[b]	.01[b]
Pain freedom	Goadsby et al, 2018[52] (ACT 2)	Proportion, 30 min	14/13	43	19.1	Absolute difference: 23.9 (14.4)	.08
Pain freedom in ≥ 50% of attacks	Silberstein et al, 2016[51] (ACT1)	Proportion, 15 min	38/47	15.8	2.1	RR 7.42 (0.93 to 59.01)[b]	.06[b]
	Goadsby et al, 2018[52] (ACT 2)	Proportion, 15 min	14/13	35.7	7.7	RR 4.64 (0.62 to 34.65)[b]	.13[b]
Headache intensity	Silberstein et al, 2016[51] (ACT1)	Mean for all treated attacks, 15 min	38/47	2.0	2.0	Mean difference: 0 (−0.34 to 0.34)[b]	.0[b]
	Goadsby et al, 2018[52] (ACT 2)	Mean change from attack onset to follow-up, 15 min	11/8	−1.7	−0.6	Mean difference: −1.10 (−1.98 to −0.22)	.01
		Mean change from attack onset to follow-up, 30 min	11/8	−1.9	−0.8	Mean difference: −1.10 (NR)	.03

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation, RR, relative risk; SE, standard error.

[a] Calculated *P* values may differ from those in the published analyses due to varying statistical techniques and rounding.

[b] Calculated using data provided.

Table 8: Summary of Subgroup Analyses for Pain-Related Outcomes, nVNS vs. Control, Acute Treatment, Chronic Cluster Headache

Pain outcome	Author, year (study)	Measurement, time	Participants, nVNS/control, n	Mean or proportion		Summary effect (95% CI or SE)	*P*
				nVNS	Control		
Response	Silberstein et al, 2016[51] (ACT1)	Proportion after first attack, 15 min	22/26	13.6	23.1	RR 0.59 (0.17 to 2.09)[b]	.41[b]
	Goadsby et al, 2018[52] (ACT2)	Mean proportion treated of attacks per person, 30 min	34/31	36.6	28.5	Absolute difference: 8.1 (8.1)	.34
Response in ≥ 50% of attacks	Silberstein et al, 2016[51] (ACT1)	Proportion, 15 min	22/26	13.6	30.8	RR 0.44 (0.13 to 1.47)[b]	.18[b]
	Goadsby et al, 2018[52] (ACT2)	Proportion, 15 min	34/31	29.4	12.9	RR 2.28 (0.8 to 6.53)[b]	.12[b]
Sustained response	Silberstein et al, 2016[51] (ACT1)	Proportion, 15 min sustained to 60 min	22/26	13.6	15.4	RR 0.89 (0.22 to 3.54)[b]	.86[b]
Pain freedom	Goadsby et al, 2018[52] (ACT2)	Proportion, 30 min	34/31	19.2	17.9	Absolute difference: 1.3 (6.5)	.76
Pain freedom in ≥ 50% of attacks	Silberstein et al, 2016[51] (ACT1)	Proportion, 15 min	22/26	4.6	15.4	RR 0.30 (0.04 to 2.45)[b]	.26[b]
	Goadsby et al, 2018[52] (ACT2)	Proportion, 15 min	34/31	8.8	6.5	1.37 (0.24 to 7.65)[b]	.72[b]
Headache intensity	Silberstein et al, 2016[51] (ACT1)	Mean for all treated attacks, 15 min	22/26	2.3	1.9	Mean difference: 0.4 (−0.7 to 0.87)[b]	.09[b]
	Goadsby et al, 2018[52] (ACT2)	Mean change from attack onset to follow-up, 15 min	25/23	−1.2	−1.0	Mean difference: −0.2 (−0.75 to 0.35)	.48[b]
		Mean change from attack onset to follow-up, 30 min	25/23	−1.5	−1.3	Mean difference: −0.2	.5

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation, RR, relative risk; SE, standard error.
[a] Calculated *P* values may differ from those in the published analyses due to varying statistical techniques and rounding.
[b] Calculated using data provided.

Duration of Headache Attack

The ACT1[51] trial evaluated the mean duration of the first cluster headache attack, as well as the mean change in attack duration from baseline (the last attack prior to randomization) to the first attack (Table 9). Both analyses were exploratory evaluations and included data only for a modified intention-to-treat population based on observed cases. Given that the mean change in attack duration from baseline was based on patient recollection for baseline data, we focused on the mean duration measure.

Overall, the duration of the first cluster headache attack was reduced by an average of 9.3 minutes among people receiving nVNS relative to controls; however, results were very uncertain with confidence intervals ranging from a 25-minute reduction in duration to a 6-minute increase. The GRADE for this body of evidence was Low, downgraded due to risk of bias and imprecision.

The magnitude of the effect size changed in the subgroup of people with episodic cluster headache (mean difference −12.8 minutes) or chronic cluster headache (mean difference −3.1 minutes), but neither of these analyses achieved statistical significance (Table 9).

Table 9: Mean Duration of First Attack, nVNS vs. Control, Acute Treatment, Cluster Headache

Author, year (study)	Measure	Subgroup	Participants, nVNS/control, n	Mean duration or mean change (SD), min		Mean difference (95% CI)[a]	P[a]
				nVNS	Control		
Silberstein et al, 2016[51] (ACT1)	Mean duration of first attack[b]	Overall	53/64	50.6 (38.3)	59.9 (47.5)	−9.3 (−24.85 to 6.25)	.24
		Episodic	34/40	48.4 (35.4)	61.2 (49.5)	−12.8 (−32.21 to 6.61)	.20
		Chronic	19/24	54.5 (43.8)	57.6 (44.8)	−3.1 (−29.73 to 23.53)	.82
	Mean change in duration from baseline to first attack[b,c]	Overall	41/53	−9.5 (51.8)	12.8 (45.5)	−22.3 (−42.34 to −2.26)	.03
		Episodic	28/36	−14.4 (59.5)	16.3 (51.5)	−30.70 (−58.43 to −2.97)	.03
		Chronic	13/17	1.0 (28.6)	5.4 (29.2)	−4.4 (−25.24 to 16.44)	.68

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; SD, standard deviation.

[a] Calculated from data provided in study.

[b] Excluded attacks with a duration of greater than 180 minutes.

[c] From the last attack before randomization (based on participant recollection) to the first attack in the randomized phase of the study.

Acute Medication Use

Only 1 study evaluated the use of rescue medication (i.e., acute medication use) within the first hour after treatment initiation for the first attack. Overall, the evidence suggested a 24% relative reduction in the use of acute medications with nVNS compared to controls, but these findings were not statistically significant. The GRADE for this body of evidence was Moderate, downgraded due to imprecision.

The study also found no statistically significant difference in acute medication use when participants were subgrouped by episodic or chronic cluster headache (Table 10).

Table 10: Rescue Medication Use in the First Hour After Treatment, nVNS vs. Control, Acute Treatment, Cluster Headache

Author, year (study)	Subtype	Participants, nVNS/control, n	Acute medication use, %		RR (95% CI)[a]	P[a]
			nVNS	Control		
Silberstein et al, 2016[51] (ACT1)	Overall	60/73	38.3	50.7	0.76 (0.51–1.12)	.16
	Episodic	38/47	42.1	48.9	0.86 (0.54–1.38)	.53
	Chronic	22/26	31.8	53.9	0.59 (0.29–1.20)	.15

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation, RR, relative risk.

[a] Calculated from data provided in study.

Adverse Events

A meta-analysis of the adverse events observed in each of the 2 acute treatment trials is shown in Figure 4. Only adverse events that occurred during the double-blind phase of the study were included.

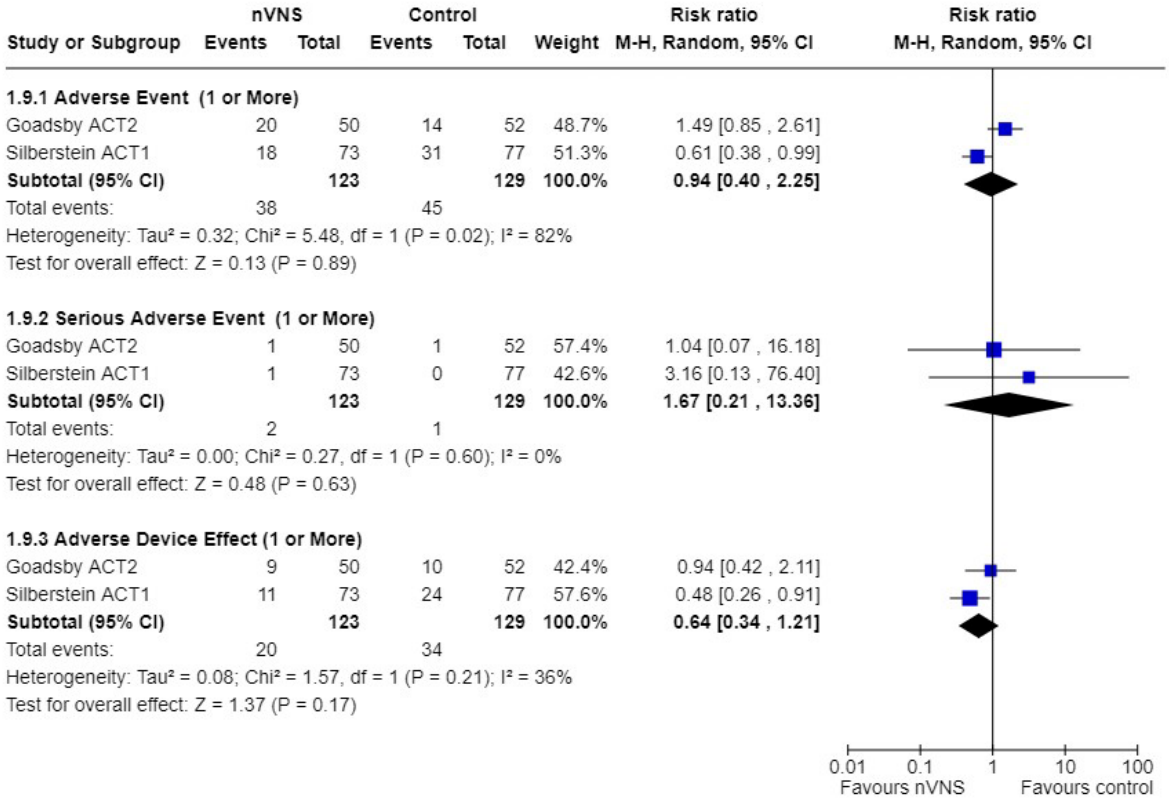

Figure 4: Meta-Analysis of Adverse Events, nVNS vs. Control, Acute Treatment, Cluster Headache

Meta-analysis of the results of 2 studies showed a risk ratio of 0.94 (95% CI 0.40–2.25) for the number of people with 1 or more adverse events, 1.67 (95% CI 0.21–13.36) for the number of people with 1 or more serious adverse events, and 0.64 (95% CI 0.34–1.21) for the number of people with 1 or more device-related adverse events with nVNS relative to control.

Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; nVNS, noninvasive vagus nerve stimulation.

Overall, we found little to no difference in the proportion of people who experienced 1 or more adverse events or 1 or more serious adverse events with nVNS compared with controls. However, the definition or classification of an adverse event was poorly reported, and between the 2 studies,[51,52] 25% to 40% of participants in each arm experienced an adverse event. Across both studies, a total of 2 participants who received nVNS reported serious adverse events (1 cluster headache and 1 severe lower abdominal back pain that had resolved), but neither was considered to be related to the device. No participant in the nVNS arm discontinued use due to a serious adverse event. The GRADE for these outcomes was Very low, downgraded due to risk of bias, inconsistency, and imprecision for adverse events, and serious risk of bias and imprecision for serious adverse events.

Limiting our analysis to events classified as device-related, we found no statistically significant difference between nVNS and controls, with a trend toward more events in the control arm. The GRADE for this body of evidence was Very low, downgraded due to risk of bias and imprecision.

Among the device-related adverse events, the most common in the ACT2 study[52] (occurring in 1 participant or more in any treatment group) were site irritation, application site paresthesia, rash and skin irritation, myalgia and myokymia. In the ACT1 study,[51] the most common device-related adverse events (occurring in 5% or more of participants in any treatment group) were application site reactions, which occurred less frequently in the nVNS group compared with controls (burning, tingling, stinging, soreness, 2.7% vs. 9.1%; skin irritation or redness, 0% vs. 11.7%). Lip or facial system events (e.g., facial drooping, twitching, or pulling) also occurred, but only in the nVNS group (11% vs. 0%). No participants in the nVNS group experienced dysgeusia or metallic taste, compared with 7% in the control arm.

Quality of Life

We identified no studies that evaluated quality of life with the use of nVNS for acute treatment of cluster headache compared with controls.

Patient Preferences

The ACT1 study[51] reported on patient satisfaction at the end of the study, based on a score of 1 (extremely satisfied) to 5 (not at all satisfied). Overall, more participants in the nVNS arm said that they were extremely satisfied, very satisfied, or satisfied with their treatment compared with the sham arm (nVNS 38.3% vs. sham 31.9%). No statistical analysis was performed, and the outcome did not undergo GRADE assessment.

Health Care Resource Use

We identified no studies that evaluated the impact of nVNS as an acute treatment on health care resource use in people with cluster headache.

Prevention – Cluster Headache

We included a single study by Gaul et al[53] (PREVA) in our analysis of nVNS for the prevention of cluster headache. This study included only participants with chronic cluster headache; no data were available for people with episodic cluster headache for any outcome evaluated. The study allowed participants the option of using the device for the acute treatment of cluster headache, but few to no data were available on acute use, so we have reported only on prevention outcomes.

Frequency of Headache Attacks

Attacks per Week

The use of nVNS plus standard of care for the prevention of cluster headache resulted in a mean change from baseline of 3.9 fewer cluster headache attacks per week compared with standard of care alone (Table 11). The GRADE for this body of evidence was Low, downgraded for risk of bias and imprecision.

Similar results were observed when the authors adjusted for the study site as a covariate (mean change −4.2 attacks, 95% CI −7.5 to −0.8; *P* = .02).

Table 11: Change From Baseline in Number of Attacks Per Week, nVNS vs. Standard of Care, Prevention, Cluster Headache

Author, year (study)	Participants, nVNS/control, n	Mean change from baseline (SE)[a]		Mean difference (95% CI)	*P*
		nVNS	Control		
Gaul et al, 2016[53] (PREVA)	45/48	−5.9 (1.2)	−2.1 (1.2)	−3.9 (−7.2 to −0.5)	.02

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; SE, standard error.

[a] Change from 2 weeks of baseline and the last 2 weeks of randomization.

In a subsequent post hoc analysis,[54] the authors further evaluated the results by individual week and found a statistically significant reduction ($P < .02$) from weeks 2 through 4 of randomization. No statistically significant differences were observed after 1 week of treatment.

Response

Gaul et al[53] defined response to treatment as the proportion of people who achieved a reduction of 50% or greater in the mean number of cluster headache attacks per week compared with baseline. Results are shown in Table 12.

Participants who received nVNS and standard of care were 4.8 times more likely to achieve response to treatment compared with those who received standard of care alone. This finding corresponds to an absolute increase in response to treatment of 32% with nVNS (95% CI 15% to 48%). The GRADE for this body of evidence was Low, downgraded for risk of bias and serious imprecision.

Table 12: Response to Treatment, nVNS vs. Standard of Care, Prevention, Cluster Headache

Author, year (study)	Participants, nVNS/control, n	Response to treatment, n (%)[a]		RR (95% CI)
		nVNS	Control	
Gaul et al, 2016[53] (PREVA)	45/48	18 (40)	4 (8.3)	4.8 (1.76–13.10)[b]

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; RR, relative risk; SE, standard error.

[a] Response was defined as the proportion of people with a reduction of 50% or greater in the mean number of cluster headache attacks per week.

[b] Calculated based on data provided in the study.

In subsequent post hoc analyses,[54] response to treatment remained higher with nVNS plus standard of care compared with standard of care alone when using response thresholds of 25% or 75%, and these findings were statistically significant ($P < .001$ and $< .009$, respectively). However, these data were limited because they evaluated only a subset of participants from the overall analysis (Appendix 5, Table A9).

Severity or Duration of Headache Attacks

The PREVA trial[53] was designed to evaluate the use of nVNS for the prevention of cluster headache, but participants in the intervention group were given the option of using the device for the acute treatment of an attack. Therefore, we were unable to determine whether preventive treatment alone affected the duration and intensity of cluster headache attacks.

The study reported that among participants who acutely treated 1 or more cluster headache attacks with nVNS (93.8%), there was no effect on attack duration or pain intensity. The authors provided no data to support these conclusions, and the results were not included in the GRADE assessment.

Acute Medication Use

The mean change in acute medication use from the last 2 weeks of the baseline period to the last 2 weeks of the randomized study period is summarized in Table 13. Overall, it is unclear which acute interventions were considered in the overall analysis, how medication use was measured, and how the use of acute medications in the nVNS arm may have been influenced by the optional use of nVNS to abort a headache (i.e., acute treatment).

Table 13: Change in Acute Medication Use, nVNS vs. Standard of Care, Prevention, Cluster Headache

Author, year (study)	Participants, nVNS/control, n	Measure	Mean change from baseline (95% CI)[a]		Mean difference (95% CI)
			nVNS	Control	
Gaul et al, 2016[53] (PREVA)	32/42	Overall	−15 (−22.8 to −7.2)	−2 (−9.4 to 5.4)	−13 (−23.38 to −2.62)[b]
		Subcutaneous sumatriptan	−4.4 (−7.6 to −1.2)	0.7 (NR)	−5.1 (NR)
		Inhaled oxygen	−10.8 (−19.4 to −2.2)	−1.8 (NR)	−9 (NR)

Abbreviations: CI, confidence interval; NR, not reported; nVNS, noninvasive vagus nerve stimulation.

[a] Number of times that acute medication was used during the last 2 weeks of randomization.

[b] Calculated from data provided in study.

The study[53] reported that people who received nVNS plus standard of care saw a large, statistically significant reduction in any acute medication use compared with baseline; people in the standard of care arm observed only a small change from baseline. Overall, people assigned to nVNS treatment used acute medication an average of 13 fewer times than those in the control group, although there was very large uncertainty surrounding the estimate. The GRADE for the body of evidence was Low, downgraded for serious risk of bias due to study design, a modified intention-to-treat analysis, and imprecision.

The study authors reported that decreased use of acute medication with nVNS treatment was driven by reductions from baseline in use of subcutaneous sumatriptan and inhaled oxygen; however, insufficient data were provided to determine the comparative effect and variance around these estimates (Table 13).

Adverse Events

The trial by Gaul et al[53] evaluated the safety and tolerability of nVNS, but detailed results were reported only for the combined randomized controlled phase of the study and the extension phase in which people in both arms used nVNS. As a result, the control group results include adverse events experienced with and without the use of nVNS. We have reported only results that could be extracted for the randomized, controlled phase of the study, as well as adverse events that were classified as device-related during both time periods.

Any Adverse Event

Overall, more people experienced 1 or more adverse events with nVNS plus standard of care (38%, 18/48) compared with standard of care alone (27%, 13/49), but these findings were not statistically significant and confidence intervals included a decrease in events (relative risk 1.41, 95% CI 0.78–2.56). [53] The GRADE for this body of evidence was Low, downgraded due to serious risk of bias and imprecision.

The severity of adverse events was not reported separately for the randomization phase, but the study authors noted that most adverse events in both groups were mild or moderate, and the most common side effects (5% or greater in any treatment group) were cluster headache attack, dizziness, headache, nasopharyngitis, oropharyngeal pain, and neck pain. The number of serious adverse events was not reported separately for the randomization phase and therefore could not be assessed.

Device-Related Adverse Events

During the randomization phase, 23% of people in the nVNS arm (n = 11) experienced 15 adverse events that were considered to be device-related. Among these, 87% were classified as being mild or moderate; severe depression and malaise were noted in 1 person. No serious adverse events were considered to be device-related.

Including data for all people who used the device (randomization and extension phases, nVNS and crossover control groups), 20 participants (20.6%) experienced device-related adverse events, including depressed mood, malaise, oropharyngeal pain, cluster headache, paraesthesia, muscle twitching, muscle spasms, feeling hot, flush, acne, pain, throat tightness, dizziness, hyperhidrosis, toothache, decreased appetite, skin irritation, erythema, facial edema, chest pain, fatigue, pruritis, musculoskeletal stiffness, and parosmia.

This body of evidence did not undergo GRADE assessment given the lack of comparator data.

Quality of Life

Quality of life was assessed by Gaul et al[53] at baseline and at the end of the treatment phase using the EQ-5D-3L tool and the 6-item Headache Impact Test (HIT-6). Results are presented in Table 14 and summarized in the text below.

Table 14: Quality of Life, nVNS vs. Standard of Care, Prevention, Cluster Headache

Author, year (study)	Measure	Participants, nVNS/control, n	Mean change from baseline		Mean difference (95% CI)	*P*
			nVNS	Control		
Gaul et al, 2016[53] (PREVA)	EQ-5D-3L index score	35/46	0.145	−0.049	0.194 (0.054–0.334)	.007
	EQ-5D-3L VAS score	35/45	9.2	0.27	8.93 (0.47–17.39)	.039
	HIT-6 score	37/45	−2.78	−0.47	−2.31 (NR)	NR

Abbreviations: CI, confidence interval; EQ-5D-3L, 3-level version of the EQ-5D; HIT-6, 6-item Headache Impact Test; NR, not reported; nVNS, noninvasive vagus nerve stimulation; VAS, visual analogue score.

EQ-5D-3L

The study by Gaul et al[53] used the 3-level version of the EQ-5D, which consists of a descriptive score and a visual analogue scale (VAS). The descriptive score comprises 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). The VAS score measures a person's overall

self-rated quality of life from 100 to 0, ranging from “the best health you can imagine” to “the worst health you can imagine.” A summary index score can be derived by weighting each of the values.[61]

The study found a statistically significant improvement from baseline in the EQ-5D-3L index score with nVNS plus standard of care compared with standard of care alone. The mean difference of 0.194 was considered clinically meaningful based on a minimally important difference of 0.074, but confidence intervals crossed this threshold. The GRADE for this body of evidence was Low, downgraded due to serious risk of bias and imprecision.

The study authors also observed an improvement in the EQ-5D-3L VAS score with nVNS plus standard of care compared with standard of care alone (mean difference 8.93, 95% CI 0.47–17.39).

HIT-6

The HIT-6 is intended to measure the impact of headaches on daily functioning, with scores ranging from 36 to 78.[62] Higher scores indicate a greater impact on a person’s life. The study by Gaul et al[53] found a greater reduction in mean change from baseline with nVNS plus standard of care compared with standard of care alone, but insufficient data were reported to assess the variance around this estimate or to determine statistical significance. Based on data for migraine, a mean reduction of −2.31 in the HIT-6 score does not meet the suggested clinically meaningful reduction of 5 points or greater.[13] Furthermore, study authors noted that the absolute mean HIT-6 scores suggested that cluster headache attacks continued to have a substantial impact on quality of life with treatment, although they did not provide data to support this.[53] The GRADE for this body of evidence was Very low, downgraded due to very serious risk of bias and imprecision.

Patient Preferences

The study by Gaul et al[53] reported patient satisfaction with treatment, which included data from people in the control group who used the nVNS device in an extended phase of the trial. Overall, 65% (62/96) of participants stated that they would recommend the device to others.

The authors noted that over 50% of participants reported some degree of satisfaction with nVNS treatment, but they did not provide further data and they did not state how satisfaction was assessed. Therefore, we were unable to assess these results using GRADE, and there is substantial uncertainty surrounding these findings.

Health Care Resource Use

No studies were identified that reported on the impact of nVNS as a preventive treatment on health care resource use in people with cluster headache.

Migraine

Characteristics of Included Studies

Five RCTs,[55-59] published in 7 studies, were included in our analysis of migraine. The characteristics of the included studies on migraine are summarized in Table 15.

Among the included studies, 1 evaluated the use of nVNS for the acute treatment of migraine[55] and 3 evaluated the use of nVNS for the prevention of migraine.[56-58] A single study by Chaudhry et al[59]

evaluated the use of nVNS for both the acute treatment and prevention of migraine. Given that outcomes associated with pain severity and functional status may be affected by such combined use and could not be attributed solely to acute treatment or prevention, we treated this study as a prevention study and have reported results only for frequency of headache.

All studies used the gammaCore nVNS device and included a sham device for the comparator arm. All of the prevention studies required 2 consecutive stimulations at the time of treatment, but 2 studies indicated bilateral use of the device,[57,59] 1 study indicated use only on the right side of the neck,[56] and 1 study indicated use on the same side of the neck, ipsilateral to the pain.[58] Three of the prevention studies indicated that the device be used 3 times a day[56-58]; the study by Chaudhry et al[59] indicated that it be used 2 times per day.

Four of the included studies[55-58] reported follow-up data during the randomized, controlled period of the study (range 4 to 8 weeks), as well as an open-label period during which people in the control group switched to nVNS for the remainder of the study. Given that an open-label period is not a true crossover design and does not include a control group, we have reported only data from the randomized, controlled periods. Similarly, we have included only outcomes for which data were reported from the comparative arm.

All studies applied a large number of exclusion criteria, which are summarized in Appendix 4.

A summary of baseline patient characteristics is presented in Table 16. The PRESTO trial[55] (acute treatment) included only people with episodic migraine. The preventive treatment trials differed in their study populations: 1 included chronic migraine,[56] 1 included episodic migraine,[56] and 2 included a combination of episodic migraine and chronic migraine with no further stratification.[57,59]

Overall, participants in each study were reported to be predominantly Caucasian (86% to 100%) and female (76% to 97%). The mean age across studies ranged from 39 years to 47 years.

Table 15: Characteristics of Studies Included in the Clinical Literature Review, Migraine

Author, year (study)	Country, sites	Sample size, n[a]	Population	nVNS indication and protocol	Intervention	Comparator	Length of follow-up
Silberstein et al, 2016[56] (EVENT)	United States, 6	59	Adults 18–65 y Chronic migraine (ICHD-2), < 50 y at onset ≥ 15 d/mo in previous 3 mo	Prevention: 2 stimulations of 2 min to right side of neck, 5 to 10 min apart, 3 times/d	nVNS	Sham	8 wk (double-blind period)
Tassorelli et al, 2018[55] (PRESTO) *Grazzi et al, 2018[63] (post hoc)* *Martelletti et al, 2018[64] (post hoc)*	Italy, 10	248	Adults 18–75 y Episodic migraine (ICHD-3B), < 50 y at onset 3–8 migraines/mo, < 15 headache d/mo	Acute treatment: within 20 min of onset, bilateral 120 s stimulation; repeat if no improvement at 15 min; optional bilateral stimulations at 120 min if not pain-free Treated up to 5 attacks and only 1 attack in 48 h	nVNS	Sham	4 wk (double-blind period)
Chaudhry et al, 2019[59]	Germany, 1	30	Adults ≥ 18 y Refractory[b] episodic migraine and chronic migraine	Acute treatment: 1 bilateral stimulation at onset of attack; additional bilateral application allowed after 15–30 min Prevention: 2 min stimulation, 2 times/d, bilaterally	nVNS and standard of care	Sham	2 mo
Diener et al, 2019[57] (PREMIUM)	Europe, 22	341	Adults 18–75 y Episodic migraine (ICHD-3B), < 50 y at onset 5–12 migraines/mo, at least 2 lasting > 4 h	Prevention: 2 consecutive bilateral stimulations, 3 times/d	nVNS	Sham	Baseline: 4 wk Follow-up: 12 wk (double-blind period)
Najib et al, 2022[58] (PREMIUM II)	United States, 27	231	Adults 18–75 y Episodic or chronic migraine, ≤ 50 y at onset 8–20 headache d/mo, at least 5 d of migraine	Prevention: 2 consecutive 2 min stimulations to same side of neck, ipsilateral to side of predominant pain, 3 times/d	nVNS	Sham	Baseline: 4 wk Follow-up: 12 wk (double-blind period)

Abbreviations: ICHD, International Classification of Headache Disorders; nVNS, noninvasive vagus nerve stimulation.

[a] Number randomized.

[b] Refractory defined as having failed at least 4 classes of preventive medications.

Table 16: Baseline Patient Characteristics of Studies Included in the Clinical Literature Review, Migraine

Author, year (study)	Migraine subtype, % episodic	Mean age, (SD), y	Male, %	Reported race or ethnicity, %	Mean no. of headache days per mo (SD)	Mean no. of migraine days per mo, (SD)	Preventive medication use, %		Acute medication use, mean (SD) or %	
							nVNS	Control	nVNS	Control
Silberstein et al, 2016[56] (EVENT)	0	39	10.2	Caucasian: 86.4 Black: 5.1 Other: 8.5	*nVNS* 20.8 (5.0) *Control* 22.3 (4.9)	NR	Not permitted in previous 30 d	Not permitted in previous 30 d	Overall: 89.8%	Overall: 89.8%
Tassorelli et al, 2018[55] (PRESTO)	100	*nVNS* 38.8 (11.0) *Control* 39.6 (11.8)	23.5	Caucasian: 100	*nVNS* 6.3 (2.3) *Control* 6.2 (2.1)	No. of attacks *nVNS* 5.4 (1.5) *Control* 5.4 (1.5)	35[a]	28.5[a]	Mean use per mo: 5.6 d	Mean use per mo: 5.3 d
Chaudhry et al, 2019[59]	63.3	46.96 (range 27–66)	3.3	NR	16.1[c]	No. of attacks: 12.4[b]	Overall sample: 30.8[b,c]		Overall sample: 88.5%[b]	
Diener et al, 2019[57] (PREMIUM)	100	*nVNS* 43.5 (11.1) *Control* 41.4 (12.3)	15.7	Caucasian: 94.6	*nVNS* 8.9 (2.6) *Control* 9.1 (2.6)	*nVNS* 7.9 (2.2) *Control* 8.1 (2.0)	Not permitted in previous 30 d	Not permitted in previous 30 d	Mean use per mo: 6.8 (2.7) d	Mean use per mo: 7.0 (2.8) d
Najib et al, 2022[58] (PREMIUM II)	59.3	*nVNS* 40.3 (13.9) *Control* 44.6 (10.7)	17.7	White or Caucasian: 90.3	*nVNS* 13.4 (4.0) *Control* 12.8 (3.7)	*nVNS* 9.2 (4.6) *Control* 9.9 (3.5)	33.9[d]	31.6[d]	Mean use per mo: 8.2 (3.5) d	Mean use per mo: 8.8 (4.0) d

Abbreviations: NR, not reported; nVNS, noninvasive vagus nerve stimulation; SD, standard deviation.

[a] Excluded those with botulinum toxin injections in last 6 mo or head or neck nerve blocks in last 2 mo. Most used were vitamin B2, topiramate, magnesium, and propranolol.

[b] Calculated from data provided in study.

[c] Most used were beta-blockers, valproic acid, selective serotonin reuptake inhibitors, selective serotonin noradrenaline reuptake inhibitors, and topiramate.

[d] Excluded people with 2 or more migraine prevention treatments, injections of onabotulinum toxin A, or calcitonin gene-related peptide-targeting monoclonal antibody drugs within the last 6 mo. Most used were topiramate, propranolol, zonisamide, gabapentin, and over-the-counter supplements.

Risk of Bias in the Included Studies

A summary of the risk of bias of included migraine studies are shown in Appendix 2.

All studies were randomized controlled trials. All studies used a sham device and blinded participants and assessors, but there is potential bias due to unblinded trainers. Incomplete outcome data was a concern across most studies: primary analyses required device use or data for each outcome, and there was high loss to follow-up during the randomization period. The PREMIUM II study[58] was greatly limited by substantial loss to follow-up, and the authors analyzed only participants who adhered to treatment (≥ 66% were adherent to treatment each week) and were enrolled for greater than 70 days. Concerns related to selective outcome reporting were noted in some studies, and many individual outcome analyses were rated at high risk of bias due to post hoc evaluation.

Acute Treatment – Migraine

The PRESTO RCT by Tassorelli et al[55] was the only study that assessed the acute treatment of migraine with nVNS relative to a sham control. Only people with episodic migraine were included in the study; no data are available for chronic migraine.

Data are based primarily on the initial published study, but additional supplementary and post hoc analyses (Grazzi et al[63] and Martelletti et al[64]) have been included for relevant outcomes that were not reported in the original paper. Only results that were evaluated during the randomized, double-blind period have been reported.

Pain

Tassorelli et al[55] evaluated pain based on a 4-point scale ranging from 0 (no pain) or 1 (mild pain) to moderate (2) or severe (3). Results at 120 minutes were analyzed and assessed using GRADE as the primary outcome measure for each outcome (see Methods).

Pain Relief: Response

Pain relief was defined as a reduction in pain score from moderate or severe to mild or no pain. Results for response rates at 30, 60, and 120 minutes after the first treated attack are summarized in Table 17.

Overall, more people who received nVNS achieved pain relief at 120 minutes after the first treated attack compared with those who received sham treatment, corresponding to a relative risk of 1.48 (95% CI 1.03–2.11). The GRADE for this body of evidence was Moderate, downgraded due imprecision because the confidence interval included clinically little to no difference in benefit.

Table 17: Pain Relief After First Treated Attack, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time measure, min	Participants, nVNS/control, n	Pain relief, %		RR (95% CI)[a]	*P*[a]
			nVNS	Control		
Tassorelli et al, 2018[55] (PRESTO)	120	120/123	40.8	27.6	1.48 (1.03–2.11)	.03
	60		35.8	24.4	1.47 (0.99–2.18)	.05
	30		26.7	18.7	1.43 (0.89–2.29)	.14

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; RR, relative risk.

[a] Calculated using data provided.

Post hoc analyses evaluating the percentage of all treated attacks that achieved pain relief are shown in Appendix 5, Table A10. Similar to the per-patient data, a greater proportion of attacks reached pain relief at 120 minutes with nVNS relative to control (35.2% vs. 24.4%; *P* = .02), but these data did not account for multiple attacks per person.

Pain Relief: Response in 50% or More of Attacks

Consistency of response was measured as the proportion of people who achieved pain relief in 50% or more of attacks at 120 minutes, among those with at least 2 treated migraine attacks. The PRESTO study[55] found that nearly 50% of nVNS users achieved consistency of response and were 1.47 times more likely to respond to treatment in 50% or more of attacks compared with those who received sham treatment (Table 18). The GRADE for this body of evidence was Low, downgraded due to risk of bias and imprecision.

Table 18: Response in ≥ 50% of Attacks, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Participants, nVNS/control, n	Response in ≥ 50% of attacks, n (%)		RR (95% CI)	*P*
		nVNS	Control		
Tassorelli et al, 2018[55] (PRESTO)	105/99	50 (47.6)	32 (32.3)	1.47 (1.04–2.09)[a]	.03[a]

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; RR, relative risk.
[a] Calculated using data reported in the study.

Pain Relief: Sustained Treatment Response

Martelletti et al[64] performed multiple additional analyses of the PRESTO trial[55] to evaluate the proportion of attacks that achieved pain relief at both 2 hours and 24 or 48 hours after treatment, without the use of rescue medication. Results for the first attack are shown in Table 19. Results for all attacks (not reported per person) are summarized in Appendix 5, Table A11.

Overall, the authors found little to no difference between nVNS and control in the proportion of people who achieved sustained pain relief at 24 or 48 hours after their first attack, although the GRADE for this body of evidence was Low, downgraded due to risk of bias and imprecision. Risk of bias was downgraded because the definition of this outcome changed from a measure of relief in all participants at 24 and 48 hours in the protocol to limiting to those who achieved response at 2 hours in the publication.

Table 19: Sustained Pain Relief After First Treated Attack, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time, h	Participants, nVNS/control, n	Sustained pain relief, %		RR (95% CI)[a]	*P*
			nVNS	Control		
Martelletti et al, 2018[64] (PRESTO)	24	75/58	77.3	79.3	0.98 (0.81–1.17)	.78
	48		69.3	71	0.98 (0.78–1.23)	.87

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; RR, relative risk.
[a] Calculated using data reported in the study.

Pain Freedom

Pain freedom was defined as the complete resolution of migraine or headache pain (pain score 0). Results for pain freedom at 30, 60, and 120 minutes after treatment completion for the first treated migraine attack are presented in Table 20. Results at 120 minutes were the primary outcome.

Overall, people who received nVNS were 42% more likely to achieve pain freedom at 120 minutes relative to sham treatment, but this finding did not reach statistical significance; confidence intervals included an 8% relative decrease in pain freedom. Study authors made similar observations when evaluating the absolute difference between groups and adjusting for baseline pain score, use of preventive therapies, and presence of aura (risk difference, 10.7%, *P* = .067). The GRADE for this body of evidence was Moderate, downgraded due to imprecision.

Table 20: Pain Freedom After First Treated Attack, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time, min	Participants, nVNS/control, n	Pain freedom, %[a]		RR (95% CI)[b]
			nVNS	Control	
Tassorelli et al, 2018[55] (PRESTO)	120	120/123	30	21.1	1.42 (0.92–2.20)
	60		20.8	12.1	1.71 (0.95–3.08)
	30		15	5.7	2.64 (1.14–6.08)

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; RR, relative risk.

[a] Percent estimates may not match those reported by the study due to the use of unadjusted data.

[b] Calculated from unadjusted data provided in the study.

Post hoc analyses evaluating the percentage of all treated attacks that reached pain freedom are shown in Appendix 5, Table A12. Similar to the per-person data for the first attack, a higher proportion of attacks reached pain freedom at 120 minutes for the nVNS group relative to controls, but results were not statistically significant (absolute difference 8.1%, *P* = .13) These data were not controlled for the number of attacks per person.

Pain Freedom in 50% or More of Attacks

Consistency of pain freedom was measured as a post hoc analysis and defined as the proportion of people who achieved pain freedom in 50% or more of attacks at 120 minutes among those with at least 2 treated migraine attacks (Table 21).

The PRESTO study[55] found that people treated with nVNS were more likely to achieve pain freedom in 50% or more of attacks compared with sham treatment alone, with an absolute (risk difference) increase of 14% (95% CI 2%–26%); this finding was statistically significant. The GRADE for the body of evidence was Very low, downgraded due to risk of bias and imprecision. Results were downgraded 2 levels due to risk of bias because this was an exploratory post hoc analysis, and it excluded participants who treated only 1 attack.

Table 21: Pain Freedom in 50% or More of Attacks, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Participants, nVNS/control, n	Pain freedom, n (%)		RR (95% CI)	*P*
		nVNS	Control		
Tassorelli et al, 2018[55] (PRESTO)	105/99	34 (32.4)	18 (18.2)	1.78 (1.08–2.94)[a]	.02

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; RR, relative risk.
[a] Calculated in Cochrane RevMan[40] using data provided.

Sustained Pain Freedom

Martelletti et al[64] performed post hoc analyses of the PRESTO trial[55] to evaluate the proportion of attacks that reached pain freedom at 2 hours and at 24 or 48 hours after treatment, without the use of rescue medication. Participants who did not achieve pain freedom at 2 hours were excluded from the analysis. Results for the first attack are shown in Table 22. Results for all attacks (not per person) are summarized in Appendix 5, Table A13.

Overall, the authors found little to no difference between nVNS treatment and control in the proportion of people who achieved sustained pain freedom at 24 hours (9.6% absolute decrease) or 48 hours (10.9% absolute decrease) after their first attack. The GRADE for this body of evidence was Very low due to risk of bias and imprecision.

Table 22: Sustained Pain Freedom After First Treated Attack, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time measure, h	Participants, nVNS/control, n	Sustained pain freedom, %		RR (95% CI)[a]	*P*[a]
			nVNS	Control		
Martelletti et al, 2018[64] (PRESTO)	24	36/26	75	84.6	0.89 (0.7–1.08)	.4
	48		58.3	69.2	0.84 (0.58–1.23)	.37

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; RR, relative risk.
[a] Calculated from data provided.

Headache Intensity

Tassorelli et al[55] reported on pain intensity in multiple publications using different measures of effect. Given that all analyses were listed as post hoc, we focused on the raw change scores reported in Martelletti et al[64] rather than percent reductions in the original article. Results for mean change in pain score from baseline to follow-up at 30, 60, and 120 minutes for the first treated attack are shown in Table 23.

At 120 minutes, mean pain scores from baseline to follow-up were reduced by 0.39 points with nVNS relative to control. The GRADE for this body of evidence was Very low, downgraded due to risk of bias (post hoc analysis and analyzed in multiple ways) and imprecision.

The study authors also reported the same trend for the mean percentage pain score reduction at 120 minutes (mean change −29.4% [nVNS −34.8%, control −5.4%], *P* = .004).

Table 23: Mean Change in Pain Score From Baseline to Follow-up for the First Treated Attack, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time, min	Participants, nVNS/control, n	Mean change from baseline (95% CI)		Mean difference (95% CI)	*P*
			nVNS	Control		
Martelletti et al, 2018[64] (PRESTO)	120	120/123	−0.62 (NR)	−0.23 (NR)	−0.39 (NE)	.011
	60		−0.51 (NR)	−0.22 (NR)	−0.29 (NE)	.029
	30		−0.34 (NR)	−0.15 (NR)	−0.19 (NE)	.074

Abbreviations: CI, confidence interval; NE, not estimatable; NR, not reported; nVNS, noninvasive vagus nerve stimulation.

Additional post hoc analyses showed a similar trend in results when evaluating mean change scores across all treated attacks (Appendix 5, Table A14).

Acute Medication Use

The PRESTO study[64] evaluated the impact of the acute use of nVNS for migraine on acute medication use. Use was measured at baseline and at follow-up, and summary measures defined as the number of acute medications used per migraine attack (Table 24). Little detail was provided on how use was defined, the time period it was measured for, or what medications were considered.

Overall, a mean reduction of 0.10 medications per attack was observed, which was not clinically meaningful and not statistically significant. The GRADE for this body of evidence was Low.

Table 24: Acute Medication Use per First Treated Attack, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Participants, nVNS/control, n	Mean medication use per attack,		Mean difference (95% CI)	*P*
		nVNS	Control		
Martelletti et al, 2018[64] (PRESTO)	120/123	Baseline: 0.86 Follow-up: 0.45	Baseline: 0.86 Follow-up: 0.55	−0.10 (NR)	.055

Abbreviations: CI, confidence interval; NR, not reported; nVNS, noninvasive vagus nerve stimulation.

Adverse Events

Adverse events were reported by the PRESTO study[55] only for the combined study periods (randomized and crossover open-label period), so we have not summarized them in our review because events occurring with the sham device and the nVNS device could not be distinguished for the sham intervention arm.

Overall, no serious adverse events occurred in either arm of the study. Two participants discontinued the study due to adverse events, both from the control group; however, the authors did not indicate the study period during which this occurred (sham vs. nVNS crossover).

Quality of Life

No studies were identified that reported on the impact on quality of life of nVNS as an acute treatment for migraine.

Patient Preferences

The PRESTO trial[55] noted more people rating treatment as "a little satisfying or better" with nVNS relative to sham (72% vs. 63.9%, significance not reported). More people who received nVNS also noted that they would recommend their device to a friend or a family member (60.2% vs. 46.7%, significance not reported).

Health Care Resource Use

No studies were identified that reported on the impact on health care resource use of nVNS as an acute treatment for migraine.

Prevention – Migraine

Frequency of Headache or Migraine

All included migraine prevention studies used frequency of migraine or headache days as the primary outcome measure. Migraine days were defined as any migraine headache occurring in a 24-hour period, and headache days were defined as any headache occurring in a 24-hour calendar period[57,58] or any day a participant recorded a headache.[56] The study by Chaudhry et al[59] did not clearly define or differentiate between headache days or migraine attacks.

Two studies measured outcomes at baseline and the last 4 weeks of the randomized period; 1 study stated that outcomes were evaluated at the end of 2 months.[56]

Migraine Days

Two studies reported the mean change in migraine days from baseline to follow-up per month (Table 25). The studies provided insufficient data to allow for meta-analysis.

People who used nVNS for prevention experienced a small reduction in migraine days per month compared with those in the control group (mean difference range, 0.5 to 0.8 fewer days); however, variance around estimates could not be determined and neither study achieved statistical significance. The GRADE for this body of evidence was Low, downgraded due to risk of bias and imprecision.

Table 25: Change in Migraine Days From Baseline to Follow-up, nVNS vs. Control, Prevention, Migraine

Author, year (study)	Participants, nVNS/control, n	Mean change from baseline in migraine days per month (95% CI)		Mean difference (95% CI)	*P*
		nVNS	Control		
Diener et al, 2019[57] (PREMIUM)	165/167	−2.26 (−2.81 to −1.72)	−1.80 (−2.32 to −1.27)	−0.46 (NR)[a]	.15[a]
Najib et al, 2022[58] (PREMIUM II)	56/57	−3.12 (NR)	−2.29 (NR)	−0.83 (NR)[b]	.23[b]

Abbreviations: CI, confidence interval; NR, not reported; nVNS, noninvasive vagus nerve stimulation.
[a] Variance was not calculated because the reported data were adjusted using regression models for treatment group, centre, presence or absence of aura, and number of migraine days at baseline.
[b] Adjusted for treatment group, centre, presence of aura, and number of migraine days at baseline.

Headache Days

Four studies[57] reported on the mean change from baseline in headache days per month with nVNS compared with control (Table 26). Insufficient data were provided to allow for meta-analysis.

Three studies[57] found that people using nVNS had fewer headache days per month compared with controls (mean difference range, 0.62 to 1.6 fewer days); however, results were uncertain and no statistically significant difference was observed in any study. The study by Chaudhry et al[59] did not report any summary effect estimates but stated no difference in the number of headache days per month (*P* = .57). The GRADE for this body of evidence was assessed as Low, downgrading due to risk of bias and serious imprecision.

Table 26: Mean Change in Headache Days, nVNS vs. Control, Prevention, Migraine

Author, year (study)	Participants, nVNS/control, n	Mean change from baseline in headache days per month (95% CI)		Mean difference (95% CI)	*P*
		nVNS	Control		
Silberstein et al, 2016[56] (EVENT)	30/29	−1.4 (−3.7 to 0.77)	−0.2 (−1.5 to 1.1)	−1.2 (−3.63 to 1.28)[b]	.56
Chaudhry et al, 2019[59]	14/12	NR[b]	NR[b]	NR	.57
Diener et al, 2019[57] (PREMIUM)	165/167	−2.73 (−3.37 to −2.09)	−2.11 (−2.74 to −1.49)	−0.62 (NR)[a]	.10[a]
Najib et al, 2023[58] (PREMIUM II)	56/57	−4.56 (NR)[c]	−3.0 (NR)[c]	−1.56 (NR)[d]	.053[d]

Abbreviations: CI, confidence interval; NR, not reported; nVNS, noninvasive vagus nerve stimulation.
[a] Variance was not calculated because reported data were adjusted using regression models for treatment group, centre, presence or absence of aura, and number of headache days at baseline.
[b] Calculated from data provided in the study.
[c] Unable to extract from figures.
[d] Adjusted for treatment group, centre, presence of aura, and number of headache days at baseline.

Response – Migraine Days

Response rates for migraine were reported by both the PREMIUM[57] and PREMIUM II[57] trials (Table 27), and were defined as a reduction in migraine days of at least 50% from baseline to the last 4 weeks of randomization.

Both studies found that a greater proportion of people achieved a response with nVNS relative to controls (from 1.4 to 2.22 greater odds). However, results from the PREMIUM[57] study were imprecise, with confidence intervals including both a benefit and an increase in migraine days. The PREMIUM II study[58] achieved statistical significance but did not provide sufficient data to estimate whether the confidence intervals around the summary estimate were clinically meaningful. The GRADE for this body of evidence was Low, downgraded due to risk of bias and imprecision.

Table 27: Proportion of Patients Achieving ≥ 50% Reduction in Number of Migraine Days, nVNS vs. Control, Prevention, Migraine

Author, year (study)	Participants, nVNS/control, n	Response (migraine days per month), %		OR (95% CI)	*P*
		nVNS	Control		
Diener et al, 2019[57] (PREMIUM)	165/167	31.9	25.0	1.4 (0.85–2.32)	.19[a]
Najib et al, 2022[58] (PREMIUM II)	56/57	44.87[b]	26.81[b]	2.22 (NR)[b]	.048[b]

Abbreviations: CI, confidence interval; NR, not reported; nVNS, noninvasive vagus nerve stimulation.
[a] Adjusted for treatment group, centre, presence or absence of aura, and number of migraine days at baseline.
[b] Adjusted for treatment group and the number of migraine days at baseline.

Chaudhry et al[59] did not report mean number of migraine days; instead, they reported the total number of attacks per month. They did not provide information about how an attack was defined or measured. Results from this assessment reported no statistically significant difference in the total number of attacks per month (*P* = .57) between nVNS and sham at baseline and follow-up.

Response – Headache Days

Silberstein et al[56] and Diener et al[57] both reported on the proportion of people who achieved response, defined as a reduction of 50% or greater from baseline in the number of headache days. Although both studies noted an increase in response for headache days with nVNS relative to control, results were highly uncertain and did not achieve statistical significance (Table 28). As well, absolute estimates of response in each arm were inconsistent between the 2 studies (10% and 28% for nVNS, 0% and 26% for control). The GRADE for this body of evidence was Low, downgraded due to risk of bias and serious imprecision.

Table 28: Proportion of Patients Achieving ≥ 50% Reduction in Number of Headache Days, nVNS vs. Control, Prevention, Migraine

Author, year (study)	Participants, nVNS/control, n	% Achieving ≥ 50% response		Relative effect	*P*
		nVNS	Control		
Silberstein et al, 2016[56] (EVENT)	30/29	10	0	RR 6.77 (0.37–125.65)[a]	NS
Diener et al, 2019[57] (PREMIUM)	165/167	28.5	25.6	OR 1.16 (0.69–1.95)[b]	.57[b]

Abbreviations: CI, confidence interval; NS, not significant; nVNS, noninvasive vagus nerve stimulation; OR, odds ratio; RR, relative risk.
[a] Calculated in Cochrane RevMan.[40]
[b] Adjusted for treatment group, centre, presence or absence of aura, and number of headache days at baseline.

Acute Medication Use

Two studies[57,58] reported on the mean change in acute medication use per day from baseline to follow-up (Table 29). Both studies reported a reduction in acute medication days (0.55 to 1.2 fewer days), but these results were not clinically meaningful or statistically significant. The GRADE for this body of evidence was Low, downgraded due to risk of bias and imprecision.

The study by Silberstein et al[56] (EVENT) did not provide comparative data for the impact of nVNS on acute medication use, but they noted that rates were comparable between groups.

Diener et al[57] reported the proportion of people who had a reduction of 50% or greater in acute medication days and found an absolute increase of 7.8% of people who achieved a response with nVNS (30.9%) compared with controls (23.1%), but this finding did not reach statistical significance (odds ratio 1.49, 95% CI 0.87–2.54; *P* = .14).

Table 29: Mean Change in Acute Medication Days, nVNS vs. Control, Prevention, Migraine

Author, year (study)	Participants, nVNS/control, n	Mean change in acute medication days from baseline		Mean difference (95% CI)	*P*[a]
		nVNS	Control		
Diener et al, 2019 (PREMIUM)[57]	165/167	−1.9 (−2.47 to −1.32)	−1.35 (−1.91 to −0.79)	−0.55 (NR)[a]	.11
Najib et al, 2022[58] (PREMIUM II)	56/57	−2.53 (NR)	−1.36 (NR)	−1.17 (NR)[a]	.11

Abbreviations: CI, confidence interval; NR, not reported; nVNS, noninvasive vagus nerve stimulation.

[a] *P* values from linear logistic regression adjusted for treatment group, presence of aura, and number of medication days in the run-in period.

Adverse Events

Meta-analyses of adverse event outcomes for nVNS compared with control are summarized in Figure 5. We included only comparative data that could be extracted for the randomized, controlled phases of the studies.

The definitions and a categorization of adverse events were poorly described in each study. Overall, there was little to no difference between nVNS and control in terms of the number of people who experienced 1 or more adverse events or 1 or more device-related adverse events. The absolute number of serious adverse events was low in both arms (< 0.01%), leading to substantial uncertainty in the effect estimate (relative risk 1.54).

Reported adverse events varied between studies. Silberstein et al[56] noted that most events were mild or moderate, and the effects observed were transient. The most reported adverse events that may have been related to the device were eye twitch, facial pain or numbness, and gastrointestinal symptoms. Najib et al[58] also noted most adverse events were mild and unrelated to nVNS treatment; the most common device-related adverse events were headache or migraine, pain at the application site, jaw pain, dysphonia, sensory disturbance, and palpitations. Neither of the 2 serious adverse events (i.e., hematoma and pyelonephritis) was related to treatment. Diener et al[57] reported only specific device-related adverse events across all study periods (including the unrandomized phase), the most common being application site pain, discomfort, rash or erythema, and dizziness. None of the device-related adverse events was considered to be serious.

The study by Chaudhry et al[59] reported on adverse events but was not included in the meta-analysis because study participants used the device for the acute treatment and prevention of migraine. Overall, study authors noted that 1 person in each group experienced a device-related adverse event (dysfunction), and 2 mild non-device-related adverse events occurred in the sham control group.

Only 2 studies commented on discontinuation due to adverse events. Silberstein et al[56] noted that no participants discontinued in either arm due to an adverse event. Diener et al[57] noted no statistically significant difference in discontinuation between the 2 groups because of adverse events (nVNS 1.2% vs. control 5.2%, *P* > .05).

The GRADE quality of evidence for each adverse event outcome was Low to Very low, downgraded for risk of bias and imprecision for all outcomes and inconsistency for adverse drug events.

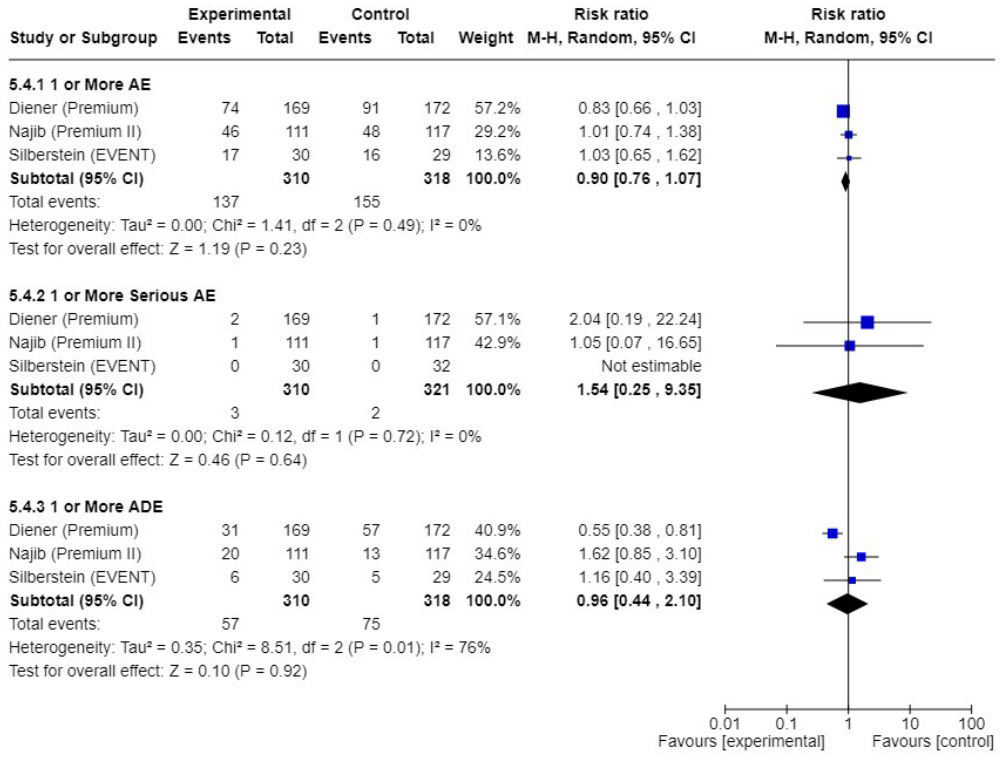

Figure 5: Meta-Analysis of Adverse Events, nVNS vs. Control, Prevention, Migraine

Meta-analysis of the results of 3 studies showed a relative risk ratio of 0.90 (95% CI 0.76–1.07) for 1 or more adverse events, 1.54 (95% CI 0.25–9.35) for 1 or more serious adverse events, and 0.96 (95% CI 0.44–2.10) for 1 or more device-related adverse events with nVNS relative to controls.

Abbreviations: ADE, device-related adverse event; AE, adverse event; CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; nVNS, noninvasive vagus nerve stimulation.

Quality of Life

No generic quality-of-life measures were reported by any of the migraine prevention studies. Two studies reported headache-specific functional measures using the Headache Impact Test-6 (HIT-6)[62] and Migraine Disability Assessment (MIDAS) scales.

The PREMIUM II trial[58] found a statistically significant improvement in HIT-6 and MIDAS scores with nVNS relative to controls (Table 30); however, results were uncertain and we were unable to calculate variance around the summary estimate. As well, these changes did not appear to be clinically meaningful based on a recommended minimum reduction of 5 points or greater.[13] The GRADE of the body of evidence was Very low, downgraded due to risk of bias and imprecision.

Chaudhry et al[59] found no statistically significant change in MIDAS scores between the 2 groups from baseline to follow-up. We did not undertake a GRADE assessment of this result for the PREMIUM II study[58] because participants used the device for acute treatment and prevention.

Table 30: Quality of Life, nVNS vs. Control, Prevention, Migraine

Author, year (study)	Measure	Participants, nVNS/standard of care, n	Quality of life, mean (SD) or %			
			nVNS	Control	Change score	*P*
Chaudhry et al, 2019[59]	MIDAS	14/12	Baseline: 3.86 (0.1) Follow-up: 3.57 (0.25)	Baseline: 3.92 (0.08) Follow-up: 3.83 (0.11)	Mean difference: −0.2 (NR)	.24
Najib et al, 2022[58] (PREMIUM II)	HIT-6	54/54	Change from baseline: −4.9 (NR)	Change from baseline: −2.3 (NR)	Mean difference: −2.6 (NR)	.025
	MIDAS	44/44	25%	9.10%	Absolute difference: 15.9%	.047

Abbreviations: CI, confidence interval; MIDAS, Migraine Disability Assessment; HIT-6, Headache Impact Test-6; NR, not reported; nVNS, noninvasive vagus nerve stimulation.

Patient Preferences and Satisfaction

Three trials reported on patient satisfaction with treatment, but they provided minimal data (Table 31). Two studies found no clear difference between the 2 groups in terms of people who reported being at least a little satisfied with their treatment. In contrast, the study by Najib et al[58] reported an absolute increase of 32% more people with nVNS being very or extremely satisfied with their treatment (*P* = .006). In addition to being underpowered, this trial analyzed only those who adhered to treatment and may be biased towards those who benefited most.

Table 31: Patient Satisfaction, nVNS vs. Control, Prevention, Migraine

Author, year (study)	Measure of satisfaction	Participants, nVNS/control, n	Satisfied, %		
			nVNS	Control	*P*
Silberstein et al, 2016[56]	At least a little satisfied with treatment	24/24	58.3	41.7	.25
Diener et al, 2019[57] (PREMIUM)	At least a little satisfied with treatment	165/167	77.5	73.5	NR[a]
Najib et al, 2022[58] (PREMIUM II)	Very or extremely satisfied with treatment	56/57	53.8	21.8	.006

Abbreviations: NR, not reported; nVNS, noninvasive vagus nerve stimulation.

[a] Authors noted similar results between studies.

Ongoing Studies

We are not aware of any ongoing studies that have potential relevance to our research question or that may affect this review. One trial evaluating nVNS for migraine was withdrawn prior to enrollment on ClinicalTrials.gov (NCT03787238).

Discussion

Cluster headache and migraine are 2 distinct types of primary headache that can cause substantial pain, disability, decreases in quality of life, and economic burden. Cervical nVNS has been proposed as a nonpharmacologic, noninvasive treatment option to prevent these headaches from occurring, as well as to reduce the pain and duration by acutely treating an attack.

Findings from this review were generally consistent with other published systematic reviews and health technology reports.[65-69] However, the present review is the most up to date, incorporating data for both cluster headache and migraine, both acute treatment and prevention, and more comprehensive outcomes to align with published guidance.[44]

Specific considerations related to cluster headache, migraine, and overall methodological considerations and limitations are outlined below.

Cluster Headache

The evidence from 1 small open-label trial[53] suggests that nVNS as an adjunct to standard care may be beneficial for the preventive treatment of chronic cluster headache by reducing the frequency of cluster headache attacks, reducing the use of acute medications and improving quality of life, but the evidence is uncertain. The evidence from 2 RCTs[51,52] suggests that when used solely for the acute treatment of cluster headache attacks, nVNS may be effective in improving response to treatment (pain relief and pain freedom) and reducing the need for additional acute medication; however, no critical outcomes achieved statistical significance and all results were uncertain.

It is important to note that all included studies on cluster headache evaluated the use of nVNS as an adjunct to standard care; therefore, the benefits observed were incremental to current treatment. As such, we do not know whether these benefits would be maintained if the device were used alone or as first-line treatment. Similarly, the single trial evaluating the preventive treatment of cluster headache[53] allowed participants the option of using the device for acute treatment of their attacks. Although our review focused on results from this trial that were related to prevention (i.e., frequency of headache), other effectiveness outcomes and adverse events may have been affected by this combined use of nVNS. However, the benefits observed for quality of life and acute medication use can likely be attributed to preventive treatment, because no differences were reported for pain intensity or duration of attack among those who used nVNS for acute treatment of their attacks, aligning with the findings for the acute treatment of chronic cluster headache.

The single study that evaluated the use of nVNS to prevent cluster headache was an open-label design and therefore at potential risk of a placebo effect given the lack of a sham control.[53] Guidelines for controlled trials in cluster headache recommend the use of a double-blind design with a sham control to account for any potential placebo effects when assessing neuromodulation devices.[70] This limitation was captured in our risk of bias assessment and contributed to the evidence uncertainty, with all outcomes receiving a GRADE assessment of Low to Very low.

Several previous reviews and health technology assessments[30,65,71,72] have focused primarily on positive conclusions for the acute treatment of cluster headache based on subgroup analyses of participants with episodic cluster headache; these analyses found larger effect sizes and greater statistical significance for response outcomes compared with the overall analysis and little to no difference in outcomes observed with chronic cluster headache. Although we included the results from these

subgroup analyses in our review and have highlighted the potential benefit for those with episodic cluster headache, we have not focused our conclusions on these subgroups because the included studies were not powered for these analyses, as is recommended by treatment guidelines.[70] Furthermore, we assessed these analyses as being at serious risk of bias, with serious imprecision for each of the outcomes.

Some reviews reported results only for acute treatment based on individual subgroup results from a combined meta-analysis of data from the ACT1 and ACT2 trials[60] that we excluded from the present review because it was neither a primary study nor a systematic review. We also noted that this analysis included data that were not published in either of the trials and had concerns related to methods for meta-analysis.

Migraine

Evidence from a single small RCT[55] suggested that nVNS for the acute treatment of episodic migraine probably increased response to treatment based on pain relief at 120 minutes for the first attack; however, this response was not sustained at 24 hours. In contrast, we found no statistically significant improvement in pain freedom at 120 minutes for the first attack, and evidence was very uncertain about pain freedom in 50% or more of attacks. Although pain relief is an important clinical outcome, International Headache Society guidance on the assessment of migraine interventions note that pain freedom is the most imperative measure of treatment success.[65,73] As well, results for a reduction in acute medication use were highly uncertain and not statistically significant.

Evidence from 4 sham-controlled trials[56-59] that evaluated the use of nVNS for the prevention of migraine suggests that nVNS may lead to small or moderate reductions in the number of migraine days and headache days, as well as response to treatment based on these reductions. However, none of these results achieved statistical significance, and the data were uncertain for all outcomes. Reductions in acute medication use were small and not clinically meaningful, and evidence for improvements in quality of life and functional status was very uncertain.

We planned subgroup analyses by migraine headache subtype based on guidance suggesting that the effectiveness of treatments may vary for people with episodic versus chronic headache.[41-43,45] Unfortunately, the included migraine studies were limited to a single subtype (i.e., only episodic or only chronic), or they used a combined population that was not stratified. Therefore, we do not know if an individual subpopulation was driving the results of the combined analysis or if effects would be observed equally in both episodic and chronic populations.

In clinical practice, limiting treatment to a specific subpopulation may be difficult because migraine diagnoses are often unstable. An estimated 2.5% to 3% of people with episodic migraine go on to develop chronic migraine, and about 26% of people with chronic migraine revert to episodic migraine after 2 years.[74,75] As well, data in migraine have recently suggested that high-frequency episodic migraines may have intensity of pain and burden similar to chronic migraine,[75,76] so treatment effects may be similar.

All included studies were in an adult migraine population; the comparative safety and effectiveness of nVNS for an adolescent population remains unknown.

Methodological Limitations and Data Gaps

Results for each question and indication were based on a small number of trials with small sample sizes. The protocols for the use of the nVNS device differed across studies and within conditions, based on the number of stimulations provided, the site of application (i.e., bilateral, left side only, or ipsilateral to pain), and the amount of time between sessions. As well, although all included studies were randomized controlled trials, the GRADE assessment of the effectiveness outcomes were generally Moderate to Very low, driven primarily by issues related to risk of bias and imprecision. Individual outcomes related to pain and frequency of headache were measured in multiple ways and differed across studies, limiting our ability to conduct meta-analyses and contributing to greater uncertainty in the effects.

Although adverse events were included in all analyses, detailed data on potential adverse events were often poorly reported for studies' comparative randomized period, and they were all uncertain. Furthermore, all studies included a highly selective patient population with extensive exclusion of participants who may have been considered at higher risk for adverse events (e.g., pregnancy, lactation, cardiovascular disease, cardiac conditions, severe hypertension, medication overuse headache). As such, it remains unclear whether the nVNS device is safe or effective for these specific patient populations.

It is unknown whether the benefits and safety of the nVNS device observed in the trials will be sustained in the long term, because follow-up periods were limited to 2 to 4 weeks for cluster headache trials and 4 to 8 weeks for migraine trials. Similarly, adverse events captured in this review were primarily those that occurred immediately after or shortly after use. Observed adverse events were generally mild to moderate and related to the application site, but potential harms with frequent or longer-term use of the nVNS device were not captured.

The mechanism of action of nVNS for treating headache has not been fully elucidated, and potential indications for the device have expanded beyond headache to include epilepsy, gastric motility disorders, depression and anxiety, and COVID-19.[77,78] As such, it is unclear how the use of nVNS in the context of headache may affect other body systems over the long term.

Our review focused on the class of cervical nVNS devices, but we identified only studies on a single device: gammaCore. This is the only nVNS device approved by Health Canada for headache, and to our knowledge no other cervical nVNS devices are available in other markets. We excluded nVNS devices applied at the external ear (i.e., auricular nVNS) because these are considered to have different effects and mechanisms of action and because they lacked approval for headache from Health Canada or the US Food and Drug Administration.

Other noninvasive neuromodulation devices (e.g., external trigeminal nerve stimulation, transcutaneous electrical nerve stimulation, transcranial magnetic stimulation) are emerging that target different peripheral nerves or the brain with transcutaneous or transcranial stimulation.[79] Of these, only 1 is known to be approved by Health Canada for the treatment of migraine (MDALL search, licence 107684). These devices were excluded from the scope of the present review because they are considered to be separate device classes that target different nerves, have different mechanisms of action, and have differing safety and effectiveness profiles.

Ontario Context

How nVNS would be placed in the Ontario clinical care pathway remains unclear. It could be used as an initial therapy, as an adjunct therapy, or as an option for people who do not respond to other

treatments. In clinical practice, Ontario neurologists and United Kingdom experts from a NICE review on gammaCore[30] indicated that nVNS would be most beneficial for people with prior treatment failure, contraindications, or intolerance to or overuse of other treatments, or for those who are averse to pharmacologic treatment and would prefer a less invasive, lower-risk treatment option (e.g., those who are pregnant or trying to conceive, younger people, those with a preference). Unfortunately, none of the studies included in this review was in a solely treatment-refractory population; none of them focused or grouped results based on these specific populations, and as previously described, they often excluded these populations from the studies.

Standard care in the included studies is generally reflective of current treatment guidelines for both cluster headache and migraine in Ontario. However, no studies included comparisons to newer acute or preventive treatment options that are funded or available in Ontario. Study participants were not taking injections of onabotulinum toxin A, gepants, or monoclonal antibodies, or they were often excluded if they were taking them. As such, it remains unclear whether these treatment options might be more effective than nVNS or if they could be used prior or as an adjunct to nVNS.

Equity Considerations

Results from the studies included in this review may not be representative of the diverse population in Ontario that experience cluster headache or migraine. None of the included studies was from Canada, and no data were reported on important PROGRESS-Plus factors such as income, socioeconomic status, or geographic region. Among the included studies, most participants were identified as White, meaning that the evidence may not capture differences that could be observed in other populations. Studies in cluster headache were primarily in men, and studies in migraine were primarily in women.

Conclusions

Results from this clinical review of the effectiveness and safety of nVNS suggests that people with cluster headache or migraine may benefit from using the device, with little to no impact on serious adverse events or device-related adverse events. However, the extent of any potential benefit is unclear, and results were generally of Very low to Moderate certainty, depending on the specific headache disorder, the indication for use, and potential subgroups.

Cluster Headache

Acute Treatment

For the acute treatment of cluster headache, treatment with nVNS compared with sham treatment plus standard care:

- May improve response to treatment, defined by pain relief (response after first attack, mean proportion achieving response, response in 50% or more of attacks and sustained response); however, we cannot exclude the possibility of no effect, and results are uncertain (GRADE: Low to Very low)
- May increase the proportion of people achieving pain freedom; however, results are uncertain and not statistically significant (GRADE: Low to Very low)
- May result in little to no difference in mean pain intensity (GRADE: Low)

- May reduce the duration of an attack, but we cannot exclude the possibility of an increase in duration (GRADE: Low)
- May reduce the use of rescue medication in the first hour after treatment; however, results are uncertain and may include a potential increase in medication use (GRADE: Moderate)
- May result in little to no difference in adverse events; however, results are uncertain (GRADE: Low to Very low)

Overall, exploratory subgroup analyses found a larger and often statistically significant benefit across outcomes for people with episodic cluster headache. In contrast, smaller effect estimates with a lack of statistical significance were observed across all outcomes for people with chronic cluster headache. However, these results are highly uncertain. We identified no data related to quality of life, functional status, or health care resource use.

Prevention

For the prevention of cluster headache, treatment with nVNS compared with standard care:

- May reduce the frequency of cluster headache attacks (reduced number of attacks per week and increased response rate; GRADE: Low)
- May reduce the use of acute medications; however, the evidence is uncertain (GRADE: Low)
- May improve quality of life; however, the evidence is uncertain (GRADE: Low to Very low)
- May not reduce the severity or duration of an attack when used in conjunction with nVNS for acute treatment; however, the evidence is highly uncertain (GRADE: not assessable)
- Does not have a statistically significant effect on adverse events (GRADE: Low)

Migraine

Acute Treatment

For the acute treatment of migraine, treatment with nVNS compared with sham treatment:

- Probably improves response to treatment, defined as pain relief (first attack and in ≥ 50% of attacks; GRADE: Moderate to Low)
- May result in little to no effect on sustained pain relief at 24 hours (GRADE: Low)
- May improve pain freedom after the first treated attack; however, we cannot exclude the possibility of no effect (GRADE: Moderate) and the evidence is very uncertain about the effect for pain freedom in 50% or more of attacks (GRADE: Very low)
- Resulted in little to no difference in sustained pain freedom; however, the evidence is very uncertain (GRADE: Very low)
- May result in small differences in the overall change in mean pain intensity scores; however, the evidence is highly uncertain (GRADE: Very low)
- May result in little to no difference in acute medication use (GRADE: Low)

There is uncertainty about the comparative effect of nVNS on adverse events, although no serious adverse events were reported. No data were identified related to quality of life, functional status, or health care resource use.

Prevention

For the prevention of migraine, treatment with nVNS compared with sham treatment:

- May slightly decrease the number of migraine days or improve response to treatment based on migraine days; however, we cannot exclude the possibility of no effect (GRADE: Low)
- May reduce the number of headache days or improve response based on headache days; however, we cannot exclude the possibility of no effect (GRADE: Low)
- May result in little to no difference for acute medication use (GRADE: Low)
- May improve quality of life or functional status; however, results are very uncertain (GRADE: Very low)
- May result in little to no difference for any adverse events; however, results are uncertain (GRADE: Low to Very low)

Economic Evidence

Research Questions

- What is the cost-effectiveness of noninvasive vagus nerve stimulation (nVNS) in addition to standard care or alone compared to standard care for the acute treatment or prevention of cluster headache in adults?
- What is the cost-effectiveness of nVNS in addition to standard care or alone compared to standard care for the acute treatment or prevention of migraine in adults and adolescents?

Methods

Economic Literature Search

We performed an economic literature search on September 13, 2023, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them until March 1, 2024. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Cost–benefit analyses, cost-consequence analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Narrative or systematic literature reviews, cost-of-illness studies, comparative or noncomparative costing analyses, letters or editorials, case reports, commentaries, abstracts, posters, unpublished studies

Participants

- Cluster headache: adults (aged 18 years and older) with cluster headache
- Migraine: adults (aged 18 years and older) or adolescents (aged 12 to 17 years) with migraine

Interventions

Inclusion Criteria

- nVNS applied at the neck for the acute treatment or prevention of headache (alone or in addition to standard care)

Exclusion Criteria

- nVNS applied at the ear (i.e., auricular branch)

Comparators

Inclusion Criteria

- Standard care (as defined by the study)
- No treatment

Exclusion Criteria

- Other invasive or noninvasive neuromodulation devices (e.g., external trigeminal nerve stimulation) or comparing different applications of the devices

Outcome Measures

- Costs
- Quality-adjusted life-years (QALYs)
- Incremental costs
- Incremental cost-effectiveness ratios (ICERs)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence,[39] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The same reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom.[80] The NICE checklist has 2 sections: the first is for assessing study applicability, and the second is for assessing study limitations. We modified the wording of the questions of the first section to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question (directly, partially, or not applicable). Next, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The economic literature search yielded 33 citations, including grey literature results and after removing duplicates, published from database inception until September 13, 2023. We identified no additional eligible studies from other sources, including database alerts (monitored until March 1, 2024). In total, we identified 5 studies that met our inclusion criteria, 4 of which were related to cluster headaches and 1 to migraine. Figure 6 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the economic literature search.

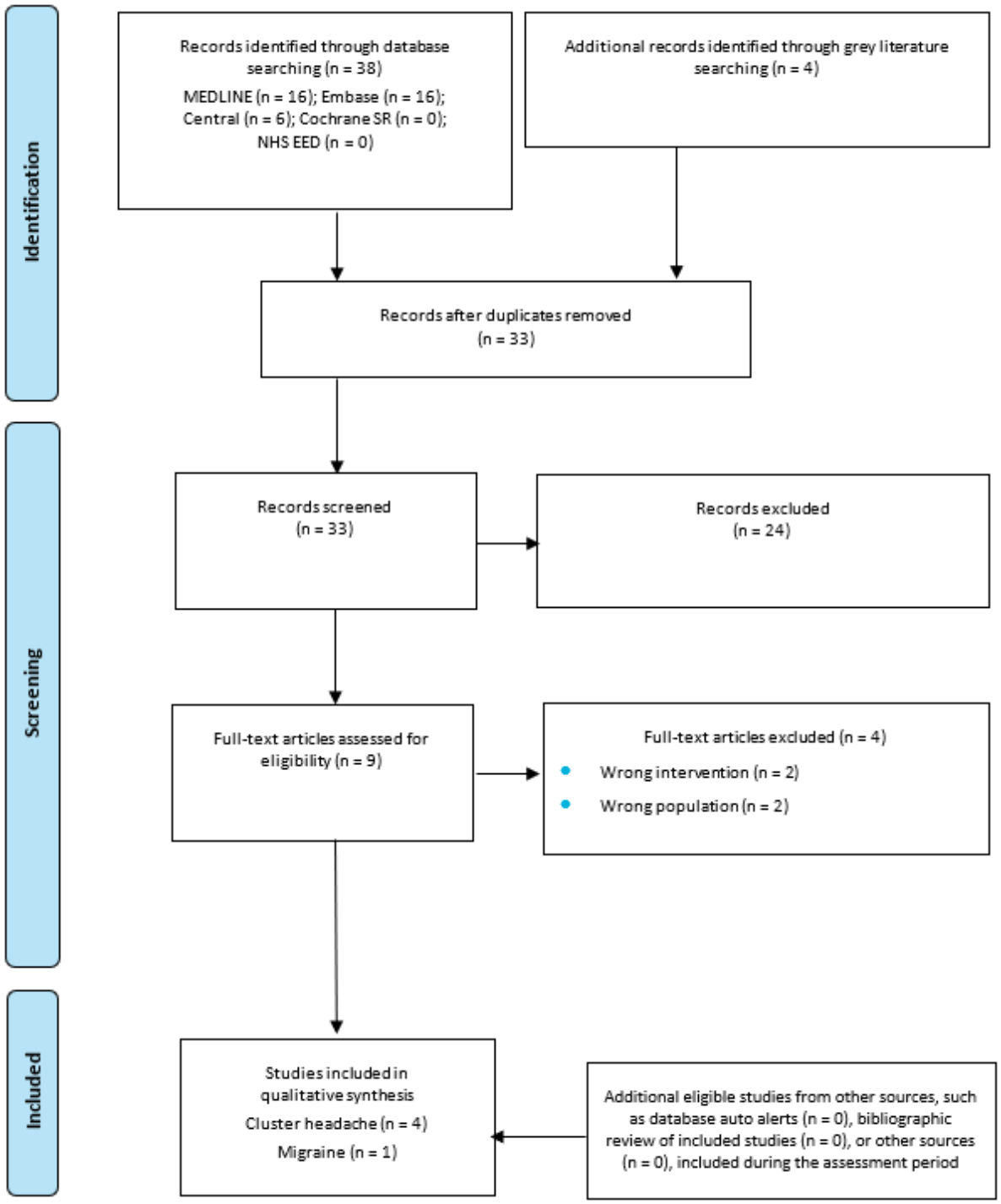

Figure 6: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic systematic review. The economic literature search yielded 33 citations, including grey literature results and after removing duplicates, published between database inception and September 13, 2023. We screened the abstracts of the 33 identified studies and excluded 24. We assessed the full text of 9 articles and excluded a further 4. In the end, we included 5 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[50]

Overview of Included Economic Studies

We identified a total of 5 studies: 3 original economic studies,[81-83] 1 medical technologies guidance from NICE in the United Kingdom (which included a costing analysis for cluster headache submitted by the manufacturer),[30] and 1 Norwegian health technology assessment that included a manufacturer-submitted cost–utility model (see Table 32).[65] All 3 of the original studies were cost–utility analyses: the first assessed a population with chronic cluster headache,[81] the second assessed a population with episodic cluster headache,[82] and the third assessed a population with episodic migraine.[83] The NICE medical technologies guidance[30] and the Norwegian health technology assessment[65] both evaluated populations with cluster headache. All studies examined the use of nVNS in adults.

The 3 cost–utility analyses[81-83] obtained the clinical effectiveness of nVNS from randomized controlled trials (RCTs).[39,51-53,84] In these RCTs, the gammaCore device was the investigational nVNS device of interest. All modelling studies were short-term, with a 1-year time horizon. All studies[81-83] were conducted from a public payer perspective. All studies found that compared with standard care alone, nVNS in addition to standard care was dominant (i.e., less costly and more effective).

Cost-Effectiveness of nVNS for Cluster Headache

Morris et al[81] conducted a cost–utility analysis to estimate the cost-effectiveness of nVNS in addition to standard care versus standard care alone for the acute treatment and prevention of chronic cluster headache. They used a 1-year Markov model that included 2 health states: responders and nonresponders. Treatment response was defined as a reduction of 50% or greater in the number of cluster headache attacks compared to baseline, according to the definition from the PREVA trial.[53] The reference case analysis was conducted from the perspective of German statutory health insurance. It showed that nVNS in addition to standard care was dominant compared with standard care alone, and in 80% of probabilistic simulations, it was cost-saving. Incremental QALY gains with nVNS in addition to standard care were 0.085 and were associated with average expected cost savings of €414.66 per patient per year (costing year unspecified). The authors also reported a secondary analysis from the perspective of the UK health care system and showed that nVNS in addition to standard care led to an additional cost of £16.52 and was associated with an incremental QALY of 0.1. In this scenario, nVNS was cost-effective at a willingness-to-pay (WTP) value of £20,000 per QALY gained, with an ICER of £166.12 per QALY gained, and nVNS was cost saving in 47% of the probabilistic simulations compared to standard care alone.

Mwamburi et al[82] conducted a cost–utility analysis to estimate the cost-effectiveness of nVNS for the acute treatment of cluster headache from a payer perspective (type of payer undefined). The authors developed a decision-tree model with 3 potential outcomes: responder, nonresponder, and failure. This study found that nVNS in addition to standard care was dominant compared with standard care alone. Incremental QALY gains with adjunctive nVNS were 0.09, and incremental costs reductions were $530 USD (2017 USD). The clinical effectiveness estimates were based on the ACT 1 and ACT2 RCTs.[51,52] These trials assessed the acute treatment of nVNS in people with episodic cluster headache and people with chronic cluster headache. In all 1-way and multiway sensitivity analyses, nVNS in addition to standard care was cost-effective at a WTP value of $20,000 USD per QALY.[82]

The NICE medical technologies guidance evaluated the acute and preventive use of gammaCore in people with episodic or chronic cluster headache.[30] This was not a health technology assessment; rather, it was a review of an evidence submission to NICE by electroCore (the manufacturer of gammaCore) that included available clinical and cost evidence, as well as a de novo cost model produced by the

manufacturer. The clinical inputs of the cost model were obtained from the PREVA RCT.[53] The aim of the NICE assessment was to provide an independent appraisal of the evidence for the use of gammaCore for cluster headache.[30] The model was a Markov model with a 1-year time horizon.[30] The analysis was conducted from the perspective of the UK National Health Service and personal services, and it examined the incremental cost-effectiveness of nVNS in addition to standard care compared with standard care alone. The model's health states were responder and nonresponder; responder was defined as having at least a 50% reduction in the number of cluster headache attacks. The main assumption was that all patients received gammaCore as a free trial for the first 3 months of use. Given this, a cost savings of £450.42 per patient was estimated with gammaCore for the acute and preventive treatment of cluster headache. The reduced use of sumatriptans and the free 3-month trial were identified as key drivers of the cost-saving results. A scenario analysis showed that if the 3-month free trial were not offered, gammaCore would become cost-incurring in the reference case, as well as in all scenarios with various definitions of responder status.

A 2023 health technology assessment[65] from the Norwegian Institute of Public Health evaluated the safety and cost-effectiveness of nVNS in addition to standard care compared with standard care alone in a cluster headache population. As part of this assessment, a cost–utility analysis was submitted by electroCore (the manufacturer of gammaCore) for the prevention of cluster headache. This model was conducted from a Norwegian healthcare perspective, with a time horizon of 1 year; it was a replication of the Markov model used in the cost–utility study by Morris et al.[81] The cost–utility analysis defined treatment response as a reduction of 50% or greater in the frequency of cluster headache attacks compared to baseline, according to the definition from the PREVA trial.[53] Similar to the cost model used in the NICE guidance,[30] a main assumption was that all patients received the intervention (gammaCore) as a free trial for the first 3 months of use. The results showed that nVNS in addition to standard care was dominant, with incremental QALY gains of 0.085 and incremental savings of 2,861 NOK.[65] The cost-effectiveness results were sensitive to the probability of discontinued response per month for nVNS and the probability of response for standard care. In a probabilistic sensitivity analysis, gammaCore had a 95% probability of being cost-effective for a WTP value of 400,000 NOK or more per QALY.

Cost-Effectiveness of nVNS for Migraine

Mwamburi et al[83] conducted a cost–utility analysis to evaluate the cost-effectiveness of nVNS for the acute treatment of episodic migraines in adults. The model was a decision tree with 3 potential outcomes: failure, partial responder, and persistent responder. The analysis was conducted from the perspective of a US payer and had a time horizon of 1 year (no discounting). The model used clinical effectiveness estimates from the PRESTO RCT.[84] In the reference case analysis, nVNS in addition to standard care was dominant compared with standard care alone. The use of nVNS in addition to standard care was associated with an incremental QALY of 0.04 and a cost reduction of $557 USD compared with standard care alone (costing year not specified). In a probabilistic analysis, more than 95% of the simulations were cost-effective at a WTP value of $40,000 USD per QALY gained. In a scenario analysis, the authors developed another model that included the use of erenumab, a monoclonal antibody, in a sequencing strategy or following acute treatment with nVNS or standard care. This strategy, in which nVNS was administered prior to the initiation of erenumab, was less costly (a savings of $3,088 USD, costing year not specified) and more effective (QALY gains of 0.05).

No studies examined the use of nVNS for the prevention of migraine or in adolescents with migraine.

Table 32: Characteristics of Studies Included in the Economic Literature Review

Author, year Country	Study design, analytic technique, time horizon, perspective, discounting	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes, mean QALYs per person	Costs, mean total costs per person	Cost-effectiveness
Morris et al, 2016[81] Germany	Study design: CUA Analytic technique: Markov state transition model Time horizon: 1 year Perspective: German statutory insurance (UK perspective as a secondary analysis) Discounting: NA	Adults with chronic cluster headache	Intervention: nVNS (gammaCore) plus standard care Comparator: standard care alone Use of nVNS: prevention Effectiveness data source: PREVA RCT[53]: gammaCore vs. standard care for 4 wk; then 4 wk of gammaCore plus standard care for all	nVNS plus standard care: 0.607 QALYs Standard care alone: 0.522 QALYs Difference: 0.085 QALYs	Euros (€) Costing year: NR nVNS plus standard care: €7,096.69 Standard care alone: €7,511.35 Difference: −€414.66 Cost of gammaCore €261 (calculated) per gammaCore device; €0.87 per dose (1 device is preloaded with 300 doses)	nVNS was dominant (i.e., less costly and more effective) Probabilistic analysis: nVNS was cost-saving in 80% of simulations Scenario analyses: nVNS was dominant in 3 scenarios that assessed the rate of response loss over time In a scenario assuming a UK payer perspective, the ICER was £166 per QALY
Mwamburi et al, 2017[82] United States	Study design: CUA Analytic technique: decision-tree model Time horizon: 1 year Perspective: payer (type of payer not identified) Discounting: NA	Adults with episodic cluster headache	Intervention: nVNS (gammaCore) plus standard care Comparator: standard care alone Use of nVNS: acute treatment Effectiveness data source: ACT1 and ACT2 RCTs[51,52]: double blind period of 1 mo Model included data related to response in retrained nonresponders; the source of this evidence was unclear	nVNS plus standard care: 0.83 QALYs Standard care alone: 0.74 QALYs Difference: 0.09 QALYs	USD ($) Costing year: 2017 nVNS plus standard care: $9,510 Standard care alone: $10,040 Difference: −$530 Cost of gammaCore: $590 per month	nVNS was dominant (i.e., less costly and more effective) Sensitivity analyses: all 1-way and multiway sensitivity analyses showed that nVNS was cost-effective at a WTP value of $25,000 per QALY The most influential factors were the cost reduction factor with gammaCore; the number of months of prescription per year; and the cost of standard care Probabilistic analysis was conducted, but the CEAC results were not presented

Author, year Country	Study design, analytic technique, time horizon, perspective, discounting	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes, mean QALYs per person	Costs, mean total costs per person	Cost-effectiveness
Mwamburi et al, 2018[83] United States	Study design: CUA Analytic technique: decision-tree model Time horizon: 1 year Perspective: payer (type of payer not identified) Discounting: NA	Adults with episodic migraine	2 models developed to examine different intervention pathways: • Primary model compared nVNS (gammaCore) plus standard care vs. standard care alone • Secondary model compared nVNS (gammaCore) plus standard care prior to erenumab prevention vs. no nVNS prior to erenumab prevention (with or without standard care) Use of nVNS: acute treatment Effectiveness data source: PRESTO RCT[84]	*Primary model* nVNS plus standard care: 0.67 QALYs Standard care alone: 0.63 QALYs Difference: 0.04 QALYs *Secondary model* nVNS followed by erenumab: 0.70 QALYs Standard care followed by erenumab: 0.67 QALYs Erenumab initiation with no nVNS or standard care: 0.65 QALYs	USD ($) Costing year: NR *Primary model* nVNS plus standard care: $9,543 Standard care alone: $10,040 Difference: −$557 *Secondary model* nVNS followed by erenumab: $10,678 Standard care followed by erenumab: $11,583 Erenumab initiation with no nVNS or standard care: $13,766 Difference: −$905 and –$2,183 Cost of gammaCore: $500 per month	Analysis comparing nVNS and standard care alone (primary model): gammaCore was dominant (i.e., less costly and more effective) Probabilistic analysis (primary model): nVNS was cost-effective in more than 95% of simulations at a WTP value of $40,000 per QALY 1-way sensitivity analyses: the most influential factors were the cost reduction factor with gammaCore, the number of months of prescription per year, and the cost of standard care
NICE, 2019[30] and supplementary materials[a] United Kingdom	Study design: cost analysis Analytic technique: Markov model (manufacturer-submitted economic model) Time horizon: 1 year Perspective: NHS and personal services Discounting: 3.5% for costs	Adults with cluster headache	Intervention: nVNS (gammaCore) plus standard care Comparator: standard care alone Use of nVNS: acute treatment and prevention Data source for effectiveness and cost-effectiveness: PREVA RCT[53] and economic model from Morris et al[81]	NR	British pounds (£) Costing year: NR gammaCore plus standard care: £3,448.45 Standard care alone: £3,898.86 Difference: −£450.42 Cost of gammaCore: £625 for 93 days of use after a free trial for the first 3 months	gammaCore resulted in cost savings of £450 per patient Sensitivity analysis: highest cost saving of £1,120 and a lowest estimate of −£103 cost incurring Sensitivity analysis: the cost saving depended on the availability of a free trial period and reduced sumatriptan use

Author, year Country	Study design, analytic technique, time horizon, perspective, discounting	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes, mean QALYs per person	Costs, mean total costs per person	Cost-effectiveness
Norwegian Institute of Public Health, 2023[65] Norway	Study design: CUA Analytic technique: Markov model (adapted from Morris et al[81]; manufacturer-submitted CUA) Time horizon: 1 year Perspective: Norwegian health care system Discounting: NA	Adults with cluster headache	Intervention: nVNS (gammacore) plus standard care Comparator: standard care alone Use of nVNS: prevention Data source: PREVA RCT[53] and economic model from Morris et al[81]	mVNS plus standard care: 0.525 QALYs Standard care alone: 0.441 QALYs Difference: 0.085 QALYs	NOK Costing year: NR gammaCore plus standard care*:* 29,494 NOK Standard care: 32,355 NOK Difference: −2,861 NOK Cost of gammaCore: 5,750 NOK for 93 days of use after a free trial for the first 3 months	gammaCore with standard care was dominant (i.e., less costly and more effective) over standard care alone Sensitivity analysis: gammaCore had a 95% probability of being cost-effective for a WTP value of ≥ 400,000 NOK per QALY

Abbreviations: CEAC, cost-effectiveness acceptability curve; CUA, cost–utility analysis; ICER, incremental cost-effectiveness analysis; NA, not applicable; NHS; National Health Service, NICE, National Institute for Health and Care Excellence; NOK, Norwegian krone; NR, not reported; nVNS; noninvasive vagus nerve stimulation; QALY; quality-adjusted life-year; RCT, randomized controlled trial; WTP, willingness to pay; UK, United Kingdom.

[a] Secondary evidence.

Applicability and Limitations of the Included Studies

Applicability

Appendix 6, Table A15, provides the results of the quality appraisal checklist for the included economic evaluations, assessing their applicability to the research questions and the Ontario context. All 5 included studies were deemed partially applicable to our research questions.

The 3 original cost–utility analyses[81-83] that assessed migraine and cluster headache had different study populations because the effectiveness data were taken from 3 different RCTs.[51-53,84] Two of the RCTs assessed nVNS as an adjunct to standard care for people with cluster headache, and 1 assessed nVNS compared to no treatment for people with migraine. This made it difficult to compare the results directly across studies. Second, none of the studies was conducted in a Canadian context[81-83]; all 3 conducted their economic analyses from a payer perspective for their respective jurisdictions (UK, US, Germany). As such, they included the use of triptans and/or inhaled oxygen in their standard care costing and modelling. However, in Ontario, inhaled oxygen for cluster headaches and migraine is not publicly funded, and several types of triptans are not covered by the Ontario Drug Benefit program (e.g., eletriptan, frovatriptan) or are available for only limited funding through the accessible access program (e.g., sumatriptan nasal spray and tablets). Therefore, the applicability of the 3 original cost–utility analyses to the Ontario context was limited.

The NICE medical technological guidance[30] compared costs only, and did not incorporate effectiveness measures into its model. The Norwegian Institute of Public Health conducted a review of existing evidence as well as an appraisal of an existing model (Morris et al[81]) that was adapted to a Norwegian perspective and submitted by the manufacturer.[65] These 2 assessments were also not directly applicable to the Ontario context.

Limitations

Appendix 6, Table A16, provides the results of the quality appraisal checklist for the included economic evaluations, assessing their limitations. A limitation of all 5 included studies[30,39,65,81-83] is that they adopted a short time horizon (all 1 year), resulting in potentially uncertain results if extrapolating the findings over the long term. However, this limitation was reasonable: the RCTs upon which the economic studies were based had short follow-up periods that ranged from 5 weeks to 4 months.[51-53,84]

Discussion

We identified 5 studies that evaluated the costs or cost-effectiveness of nVNS for the treatment of cluster headache and migraine. Four cost-effectiveness studies – 3 assessing cluster headache[65,81,82] and 1 assessing migraine[83] – found that nVNS in addition to standard care was dominant (i.e., less costly, and more effective) compared with standard care alone. One cost study that assessed cluster headache found that nVNS in addition to standard care was cost saving compared to standard care alone.[30] All of the included economic studies had a 1-year time horizon. The results were sensitive to several factors, including the cost of standard care, the cost reduction factor with the use of nVNS, and whether the device was offered at no cost for a 3-month trial period.

The randomized controlled trials (PREVA, PRESTO, ACT 1, and ACT2)[51-53,84] used to populate the 5 included economic studies[30,65,81-83] had trial lengths ranging from 5 weeks to 4 months. The extrapolation of data from these trials to a 1-year time horizon was assumed to be appropriate.

However, there was a considerable amount of uncertainty in the evidence, and the internal validity of the published economic evaluations was limited by the methodological limitations of the currently available RCTs. All of the included economic studies were conducted outside of the Canadian context (i.e., UK, US, Germany, Norway), so their generalizability to the Canadian or Ontario context is limited. Therefore, all 5 included studies were partially applicable to our research questions and the Ontario context.

Equity Considerations

Results from the included economic studies may not be representative of the Ontario population. Some of the standard care treatments included in these economic studies are not publicly funded in Ontario (e.g., inhaled oxygen).

Strengths and Limitations

Our economic literature review had several strengths. We conducted a thorough review of the existing economic evidence related to nVNS, identifying studies from multiple jurisdictions (UK, US, Germany, and Norway). We evaluated the applicability of the identified studies to the Ontario context and critically appraised the quality of the studies. An important limitation of our review was that all included studies used just 1 specific nVNS device (gammaCore by electroCore). This limitation is noteworthy, because other devices in the nVNS class might produce varied cost-effectiveness outcomes that our review did not encompass.

Conclusions

We identified 5 studies that evaluated the costs or cost-effectiveness of nVNS for the treatment of cluster headache and migraine. In general, all studies found that nVNS in addition to standard care was dominant (i.e., less costly and more effective) or cost saving compared with standard care alone. These studies were partially applicable to our research question and had some limitations. The generalizability of the results of these studies to the Ontario context is limited.

Primary Economic Evaluation

The published economic evaluations identified in the economic literature review addressed the intervention of interest, but none of them were directly applicable to our research question or conducted from a Canadian perspective.

Based on the findings of the clinical evidence review, we developed 2 economic models: 1 for the prevention of cluster headache in adults and 1 for the prevention of migraine in adults and adolescents. We did not develop a model for the acute treatment of cluster headache or migraine because of limited data.

- For the acute treatment of cluster headache, no data related to quality of life were identified to support economic modelling. For the prevention of cluster headache, the clinical evidence showed that nVNS treatment may reduce the frequency of cluster headache attacks (GRADE: Low), may reduce the use of acute medications (GRADE: Low), and may improve quality of life (GRADE: Low to Very low). Utility data for each treatment arm were available from the clinical trials.
- For the acute treatment of migraine, the clinical outcomes could not be easily translated into QALYs. Therefore, we did not develop a model for the acute treatment of migraine. For the prevention of migraine, the clinical evidence suggested that nVNS treatment may slightly decrease the number of migraine days (GRADE: Low) or may improve response to treatment based on migraine days (GRADE: Low). Health state utility values for migraine were available from the literature.

Research Questions

- What is the cost-effectiveness of noninvasive vagus nerve stimulation (nVNS) in addition to standard care compared with standard care alone for the prevention of cluster headache in adults from the perspective of the Ontario Ministry of Health?
- What is the cost-effectiveness of nVNS in addition to standard care compared with standard care alone for the prevention of migraine in adults and adolescents from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[85] The content of this report is based on a previously developed economic project plan.

Type of Analysis

We conducted probabilistic cost–utility analyses as recommended by the Canadian Agency for Drugs and Technologies in Health guidelines for economic evaluations.[86] We reported the results as incremental costs per quality-adjusted life-years (QALYs) gained.

In addition to the cost–utility analyses, we also conducted cost-effectiveness analyses where outcomes were expressed in natural units, including number of cluster headache attacks and number of migraine days.

Populations of Interest

Cluster Headache

One of our populations of interest was adults with cluster headache. Cluster headache can be episodic or chronic, depending on the remission duration between attacks.[87] People with chronic cluster headache have persistent headache attacks that occur for more than 1 year without remission, or with a remission period that lasts less than 3 months without preventive medication. Chronic cluster headache occurs in 15% to 20% of the cluster headache population.[87] In episodic cluster headache, attacks are separated by remission periods of greater than 3 months. Episodic cluster headaches are more frequently diagnosed compared to the chronic type. Episodic cluster headache can later become chronic, and vice versa. The natural history of cluster headache is unpredictable.[88]

We based the population of our economic model for cluster headache on the PREVA randomized controlled trial (RCT), which compared nVNS in addition to standard care with standard care alone.[53] The study included only people with chronic cluster headache. Our model used the weighted average age (43.8 years) and the proportion of male participants (69%) from the 2 treatment arms of the PREVA RCT. The mean time since the onset of chronic cluster headache in this population was approximately 5 years.

Migraine

Our other population of interest was adolescents (age 12–17 years) and adults (age 18 years or greater) with migraine. Depending on the frequency and duration of attacks, migraines can be categorized as episodic or chronic. Chronic migraine is defined as a headache that occurs on 15 or more days per month for more than 3 months, with migraine headache features on at least 8 days per month.[89] Migraines that occur on fewer than 15 days per month are considered to be episodic.

We based the population of our economic model for migraine on the PREMIUM RCT,[57] which included people with episodic migraine. Our model used the weighted average age (42.44 years) and the proportion of female participants (84.12%) from the 2 treatment arms of the same RCT.

We did not conduct a primary economic analysis for chronic migraine because of limited data. Among the 4 preventive trials identified in the clinical evidence review, only 1 (PREMIUM II) included people with chronic migraine,[58] but this study was greatly limited by substantial loss to follow-up. The other studies included a combination of people with episodic migraine and people with chronic migraine, but without further stratification.

Perspective

We conducted the reference case analysis from the perspective of the Ontario Ministry of Health. We also considered a societal perspective in a scenario analysis to capture costs related to productivity loss and patients' out-of-pocket costs, because cluster headache and migraine both affect a primarily working-age population and some commonly used treatments (e.g., inhaled oxygen) are not publicly funded.

Interventions and Comparators

We conducted evaluations for nVNS in addition to standard care compared with standard care alone. Table 33 summarizes the interventions evaluated in the economic models.

Table 33: Interventions and Comparators Evaluated in the Primary Economic Models

Intervention	Comparator	Population	Outcome
nVNS in addition to standard care for the prevention of cluster headache	Standard care alone	Adults with cluster headache	Total costs, number of cluster headache attacks, cost per cluster headache attack avoided, QALYs, ICERs (i.e., cost per QALY gained)
nVNS in addition to standard care for the prevention of migraine	Standard care alone	Adults (aged ≥ 18 y) and adolescents (aged 12–17 y) with migraine	Total costs, number of migraine days, cost per migraine day avoided, QALYs, ICERs (i.e., cost per QALY gained)

Abbreviations: ICER, incremental cost-effectiveness ratio; nVNS, noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.

Cluster Headache

Standard Care

We included the costs of preventive treatment in the model. The most commonly used preventive treatment for cluster headache is verapamil,[12] although this medication has potential for adverse effects and cardiac impacts, and it requires regular monitoring with electrocardiogram when given at higher doses. Other medications such as lithium, warfarin, melatonin, or topiramate can also be used to prevent cluster headache,[16] but some of them are used off-label in Canada for this purpose. For simplicity, we used verapamil to represent the costs of standard care for prevention of cluster headache. Because nVNS is used in addition to standard care for the prevention of cluster headache, we assumed that the costs of preventive medication would cancel each other out.

We also included the costs of acute treatment in the model because the use of nVNS as a preventive treatment may decrease the use of acute medication. First-line acute treatment options are triptans (administered subcutaneously or as a nasal spray) and oxygen inhalation therapy, used alone or in combination.[12] See Cost Parameters, Cluster Headache, for more details.

nVNS

Based on instructions from the manufacturer[90] for prevention of cluster headache, nVNS can be self-administered (or administered by a carer) 2 times per day (morning and night), consisting of 2 stimulations lasting 2 minutes each. The first daily treatment should be administered within 1 hour of waking, and the second daily treatment should be administered at least 7 to 10 hours after the first.[90] In the PREVA study, nVNS was used in addition to standard care for the prevention of cluster headache.[53]

Migraine

Standard Care

Multiple pharmacological treatments are available for migraine, and decisions about first-line therapy are individualized to the patient. Common first-line treatments for adults include beta-blockers

(e.g., propranolol, nadolol, metoprolol) and tricyclic antidepressants (e.g., amitriptyline). Other pharmacological options include antiepileptics (e.g., topiramate, gabapentin) or other blood pressure medications (e.g., verapamil, candesartan). Botulinum toxin type A is also approved in Canada for people with chronic migraine. For the economic model, we obtained the costs of preventive treatment for migraine from a 2018 Ontario burden of illness study by Amoozegar et al.[91] Because nVNS is used in addition to standard care for the prevention of migraine, we assumed that the costs of preventive medications would cancel each other out.

We also included the costs of acute treatment in the model because acute migraine treatment may include different pharmacological options, such as nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, ergots, and possibly opioids. See Cost Parameters, Migraine, for more details.

nVNS

Based on instructions from the manufacturer[90] for the prevention of migraine, nVNS can be self-administered (or administer by a carer) 2 times per day (morning and night), consisting of 2 stimulations lasting 2 minutes each. The first daily treatment should be administered within 1 hour of waking, and the second treatment should be administered at night.

Time Horizon and Discounting

We used a 1-year time horizon in our reference case analysis. Most of the clinical trials identified in our literature search[53,84] had very short durations, with a 4-week randomization phase and follow-up periods of 4 weeks to 4 months. Therefore, we extrapolated the effectiveness of nVNS beyond the trial period using assumptions. Because the time horizon of the reference case was 1 year, we did not apply a discount rate to cost or effectiveness outcomes (e.g., QALYs). In a scenario analysis using a 2-year time horizon, we applied discounting at a rate of 1.5% annually to both cost and effectiveness outcomes.

Main Assumptions

The main assumptions of both models (cluster headache and migraine) were as follows:

- Adverse events associated with the use of nVNS for luster headaches or migraine are generally mild and would not require hospitalization or treatment (see clinical evidence review).
- There is no evidence of a sustained long-term benefit with nVNS use. In the reference case, we assumed that people would continue to use nVNS treatment after the trial period and would experience the same average effects observed in the clinical trials. However, in a scenario analysis, we followed the recommendation from the NICE medical technological guidance[30] that treatment with nVNS should be stopped if patents did not experience any reduction in symptoms in the first 3 months. For this scenario, we assumed that only responders – defined using the PREVA RCT[53] definition for cluster headache (i.e., the proportion of people who experienced a reduction of 50% or greater in the mean number of cluster headache attacks per week) and the PREMIUM RCT[57] definition for migraine (i.e., the proportion of people who experienced a reduction of 50% or greater in migraine days from baseline to the last 4 weeks of randomization) – would continue to use nVNS over the long term (i.e., after 3 months), and these people would experience benefits similar to what was observed in the clinical trials. We assumed that nonresponders would discontinue

nVNS treatment and that their clinical outcomes would be the same as for those receiving standard care alone.

Model Structure, Clinical Parameters, Utility Parameters, and Cost Parameters

Model Structure, Cluster Headache

We used a simple Markov model to estimate the costs and QALYs associated with the intervention and comparator. The model has 2 health states: alive (and being treated to prevent cluster headache) and dead (Figure 7). Patients in the alive state would receive nVNS in addition to standard care (i.e., the new intervention) or standard care alone (i.e., the comparator). Standard care includes both acute treatment and prevention. Depending on the treatment arm, people in the alive state would incur different costs and utilities (i.e., health-related quality of life), and experience cluster headache attacks at different frequencies, as observed in the clinical trial. Because the natural history of cluster headache is unpredictable, for simplicity we assumed that the frequency of cluster headache attacks (i.e., the number of attacks per 4 weeks) for each treatment arm would be consistent with trial observations, based on the PREVA RCT.[53] Patients in the alive state could remain alive or transition to the dead state (due to background all-cause mortality) every 4 weeks, which represented the length of a model cycle. We estimated the proportion of people transitioning to the dead state using survival estimates from the 2022 Ontario Life Tables.[92] We assumed no excess mortality due to underlying conditions. The model time horizon was 1 year, considering that the clinical trials of nVNS were typically conducted over short durations.[51-53]

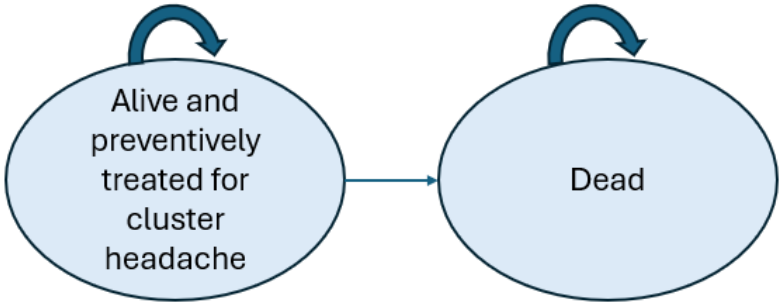

Figure 7: Model Structure, Cluster Headache

The model used for the primary economic evaluation. People in the alive state would receive nVNS in addition to standard care or standard care alone. They could remain alive or transition to the dead state (due to background all-cause mortality) every 4 weeks, which represented the length of a model cycle.

Clinical Parameters, Cluster Headache

Table 34 summarizes the clinical parameters used in the economic model for cluster headache.

Table 34: Clinical Parameters Used in the Economic Model, Cluster Headache

Clinical parameter	Mean[a]	Distribution	Reference
Number of cluster headache attacks per 4 weeks at baseline	67.3 (SE 6.3)	Normal	Gaul et al, 2016[53] (PREVA); clinical evidence review, Table 2
Change from baseline in number of cluster headache attacks per week with nVNS	–3.9 (95% CI –7.2 to –0.52)	Normal	Gaul et al, 2016[53] (PREVA); clinical evidence review, Table 11
Reduction in subcutaneous sumatriptan use	61%	Beta	Gaul et al, 2016[53] (PREVA)
Reduction in inhaled oxygen use (societal perspective only)	62%	Beta	Gaul et al, 2016[53] (PREVA)

Abbreviations: CI, confidence interval; nVNS; noninvasive vagus nerve stimulation; SE, standard error.

[a] For distributions where the 95% CI was not reported, we assumed that the SE was 15% of the mean.

Based on the clinical evidence review, the number of cluster headache attacks at baseline for the nVNS treatment arm was 67.3 over 4 weeks. The use of nVNS in addition to standard care for the prevention of cluster headache resulted in a mean change from baseline of 3.9 fewer attacks per week compared with standard care alone (95% confidence interval [CI] –7.2 to –0.52; see clinical evidence review, Table 11). The GRADE quality of evidence for this outcome was Low. This would mean 15.6 fewer cluster headache attacks over 4 weeks compared to standard care alone, or a 23% reduction from baseline.

We also considered the impact of nVNS on acute medication use. Based on the clinical evidence review, the PREVA study[53] reported that people who received nVNS in addition standard care had a large reduction in acute medication use compared to baseline (−61% in subcutaneous sumatriptan use and −62% in inhaled oxygen use, societal perspective only); people in the standard care arm observed only a small change from baseline (see clinical evidence review, Table 13). In the clinical evidence review, the GRADE quality of evidence associated with the outcome of acute medication use was Low.

Treatment-Related Adverse Events

Based on information from the manufacturer (electroCore), the gammaCore nVNS device is well tolerated, and those treated with gammaCore have not experienced any serious treatment-related side effects.[93] Most side effects are mild, occur when using the device, and resolve on their own. The most common side effects include discomfort and redness at the application site, as well as dizziness (reported by more than 1% of people who participated in gammaCore studies). This information is generally consistent with the adverse events reported in published randomized controlled trials.[16] See the clinical evidence review, Figures 4 and 5, for meta-analyses of safety and adverse events associated with nVNS use.

Adverse events associated with certain standard care treatment options for migraine and cluster headache are well documented. The use of sumatriptan succinate injections, for instance, may lead to pain at the injection site, nausea, drowsiness, and other symptoms.

Utility Parameters, Cluster Headache

A health state utility represents a person's preference for a certain health state or outcome, such as cluster headache or migraine. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health).

We performed a targeted literature search in MEDLINE for health state utility values associated with nVNS on September 27, 2023, to retrieve studies published from database inception until the search date. We based the search on the population and intervention of the clinical search strategy with a methodologic filter applied to limit retrieval to health state utility values.[94] See Appendix 1 for our literature search strategies, including all search terms.

The target health state utility value literature search yielded 12 studies, of which 3 reported relevant utilities. All 3 of these utility sources were original economic studies[81-83] already identified in our economic evidence review. However, although the original economic studies had reported utilities, we were unable to find the utility data from the reported source (the clinical studies), which the original economic studies cited. Due to uncertainty surrounding the sourcing of these utility values, we did not use the previously reported utilities[82,83] for our analysis.

For the cluster headache model, we identified 2 sources of utility inputs: Pietzsch et al[95] (which provided the baseline utility estimate for people with cluster headache and receiving standard care only), and the PREVA RCT (which reported utility improvement from baseline as a result of using nVNS).[53]

The PREVA RCT[53] assessed the use of nVNS in addition to standard care for the prevention of chronic cluster headache. It was the only RCT that reported quality-of-life outcomes using EQ-5D-3L index scores, which can be directly converted to health utilities in economic evaluations. It showed that at the end of the randomized phase (4 weeks), there was a statistically significant improvement from baseline in the EQ-5D-3L index score for nVNS in addition to standard care compared with standard care alone.[53] This outcome was also examined in the clinical review and the GRADE quality of the evidence was Low (clinical evidence review, Table 14). Patients receiving nVNS in addition to standard care continued to have improved EQ-5D-3L index scores at the end of the extension phase (8 weeks). However, people in the control arm crossed over to receive nVNS during the extension phase, so the difference between the nVNS and control arms could not be calculated.

Changes in utilities between baseline and the randomized or extension phases in the PREVA trial[53] are described below:

- EQ-5D-3L index score changes from baseline to randomized phase (4 weeks):
  - nVNS in addition to standard care: 0.145
  - Standard care alone: −0.049
  - Mean difference: 0.194 (95% CI 0.054–0.334)
- EQ-5D-3L index score changes from baseline to extension phase (8 weeks):
  - nVNS in addition to standard care: 0.155
  - Standard care alone crossed over to receive nVNS in addition to standard care: 0.078.

Pietzsch et al[95] assessed the cost-effectiveness of sphenopalatine ganglion stimulation for the treatment of cluster headaches compared with standard medical management from the perspective of the German

statutory health insurance system. From this study, we obtained a baseline utility value of 0.548 for people with cluster headache. Although the intervention used in this study was outside the scope of the current health technology assessment, the baseline utility value was applicable for our purposes because it was for a similar patient population.

Using the inputs above, we estimated the utility values of people receiving nVNS in addition to standard care and standard care alone (Table 35).

Table 35: Utilities Used in the Economic Model, Cluster Headache

Parameter	Mean EQ-5D index score[a]	Distribution	Reference
Baseline utility for people with cluster headache	0.548 (SE 0.082)	Lognormal	Pietzsch et al, 2015[95]
Change in EQ-5D-3L Index score from baseline to end of randomized phase (4 weeks), standard care alone	−0.049	Fixed	Gaul et al, 2016[53] (PREVA)
Difference in utility between the 2 arms at 4 wk	0.194 (95% CI 0.054–0.334)	Lognormal	Gaul et al, 2016[53] (PREVA)

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; SE, standard error.

[a] For distributions where the 95% confidence interval was not reported, we assumed that the standard error was 15% of the mean.

To estimate the potential impact of nVNS on a person's quality of life beyond 4 weeks, we made a simplifying assumption in the reference case: that the utility of the nVNS arm would remain constant over the entire time horizon. We used alternative assumptions in scenario analyses, such as assuming a reduced utility benefit (75%).

Cost Parameters, Cluster Headache

We obtained cost inputs from standard Ontario sources, published literature, and clinical experts. We obtained physician fees from the Ontario Schedule of Benefits for Physician Services[96] and laboratory costs from the Ontario Schedule of Benefits for Laboratory Services.[97] Costs related to nVNS devices were obtained from the manufacturer. All costs are reported in 2024 Canadian dollars. When the most recent cost inputs were not available, we used the Statistics Canada Consumer Price Index[98] to adjust costs to 2024 Canadian dollars.

Cost of the nVNS Device

Table 36 summarizes the cost of the nVNS device. According to the manufacturer, the price for gammaCore is $1,674 USD for a 93-day starter kit and $1,055 USD for a 93-day refill ($2,206 CAD and $1,390 CAD, respectively, using the conversion rate from July 2023 of 1 USD = 1.32 CAD). We assumed that 4 prescriptions (1 initial prescription plus 3 refills) would be appropriate for 1 year. According to communications with the manufacturer (electroCore, email communication, June 2023), training for the device is provided at no cost so we did not include the costs of training in our analysis.

Table 36: Costs Used in the Economic Model, Cluster Headache

Variable	Unit cost, $[a]	Quantity per year	Reference
Initial prescription of the nVNS device (93 days)	$2,206[b]	1	electroCore[c]
Refills (93-day periods)	$1,390[b]	3	electroCore[c]
Total cost per year	$6,376	–	Calculated based on unit cost

All costs expressed in 2024 Canadian dollars.

[a] The cost of the device was assumed to be fixed.

[b] Converted from the price in US dollars using a conversion rate of 1 USD = 1.32 CAD.

[c] electroCore, email communication, June 2023.

Cost of Monitoring, and Medication, and Productivity Loss

Table 37 presents the costs of monitoring, medication, and productivity loss (societal scenario analysis only) for standard care for cluster headache.

Table 37: Costs of Monitoring, Medication, and Productivity Loss, Cluster Headache

Cost	Cost per 4 wk, Ministry of Health perspective	Cost per 4 wk, societal perspective	Distribution	Reference
Monitoring: neurologist or headache specialist visit and ECG for verapamil use	$14.18	$25.95	Normal	Schedule of Benefits (A185 + G310, G313)[96]
Acute medication: sumatriptan succinate injection	$132.27	$549.00	Normal	Ontario Drug Benefit formulary for unit costs[99]; frequency based on NICE medical technologies guidance[30]
Acute medication: inhaled oxygen (societal perspective only, scenario analysis)	$0.00	$608.15	Normal	O'Brien et al, 2017[100]
Preventive medication: verapamil	$46.16	$192.00	Normal	Ontario Drug Beneft formulary for unit costs[99]; frequency based on treatment guidelines[12] (80 to 240 mg BID)
Productivity loss (societal perspective only, scenario analysis)	$0	$653.75	Normal (hourly wage)	Calculated based on Ford et al, 2018,[101] and average hourly wage in Ontario[102]

Abbreviation: BID, twice a day.

All costs are expressed in 2023 CAD. All parameters were modelled as fixed (i.e., no assigned distributions).

Abbreviations: ECG, electrocardiogram; NICE, National Institute for Health and Care Excellence.

Cost of Monitoring and Medication

We presented the costs (in 2023 CAD) from both a Ministry of Health perspective and a societal perspective. In the Ministry of Health perspective, we assumed that 24.1% of people were covered under the public drug plan.[103] We did not include inhaled oxygen in the Ministry of Health perspective, but we did include it in the societal perspective. The total costs of acute and prevention medications per 4 weeks were $132.27 and $46.16, respectively, from a Ministry of Health perspective. From a societal perspective, the total costs per 4 weeks of acute and preventive medications were $1,157.15 and $192.00, respectively.

Our assumptions for these calculations were as follows:

- We assumed that 1 visit per year to a neurologist or headache specialist would be appropriate (P. Cooper, MD, email communication, August 2023), and that people receiving nVNS in addition to standard care or standard care alone would have the same number of visits. For the societal perspective, we included additional costs, such as time off work to attend doctor visits and parking costs.
- A 2016 International Delphi study conducted by Koppen et al[104] for cardiac monitoring of high-dose verapamil in people with cluster headache found that experts in cardiac rhythm disorders agreed on pretreatment electrocardiogram (ECG) monitoring but did not reach a consensus on ECG monitoring during high-dose verapamil treatment. We assumed that 1 ECG would be performed each year to monitor people receiving high-dose verapamil treatment.
- We assumed that sumatriptan succinate injection would be the most commonly used medication for the acute treatment of cluster headache. A clinical expert advised that to avoid medication overuse, triptans should be used 9 or fewer days per month (P. Cooper, MD, email communication, August 2023). People with cluster headache may need a triptan a day for the first 3 weeks at the onset of the headaches.
- A clinical expert advised that inhaled oxygen is recommended for use in all people for acute treatment (P. Cooper, MD, email communication, August 2023). However, inhaled oxygen is not publicly funded for the acute treatment of cluster headaches in Ontario[105]; as such, we included its cost only in the societal perspective.
- We assumed that verapamil would be the most commonly used medication for the preventive treatment of cluster headache, based on treatment guidelines[12] and clinical expert opinion (P. Cooper, MD, email communication, August 2023).

Based on the PREVA RCT,[53] we estimated that people receiving nVNS in addition to standard care would have a 61% reduction in the use of subcutaneous sumatriptan injections and a 62% reduction in the use of inhaled oxygen (applicable to the societal perspective scenario analysis only).

Cost of Productivity Loss (Scenario Analysis)

In a scenario analysis, we considered the costs of productivity loss due to cluster headache from a societal perspective, using the human capital approach. We estimated the costs of productivity loss based on a US study by Ford et al.[101] The study used administrative inpatient and outpatient data to identify 3 subgroups of people with cluster headache: those with short-term disability related to cluster headache, those with absenteeism from work due to cluster headache, and those with both. The authors found that among people with cluster headache in the subgroup with absenteeism and short-term disability (n = 139), the average person lost 256 hours of productivity per year. We multiplied this figure by the average hourly pay rate in Ontario to estimate the cost of productivity loss in a year for people receiving standard care only (256 hours per year × $33.25 CAD per hour = $8,498.70 per year, or $653.75 per 4 weeks).[102]

For people receiving nVNS in addition to standard care, we estimated that there would be a 22% reduction in the costs of productivity loss. We based this estimate on the reduced the number of cluster

headache attacks observed in the PREVA RCT,[53] which reported that the use of nVNS in addition to standard care for the prevention of cluster headache resulted in a mean change from baseline of 3.9 fewer cluster headache attacks per week compared with standard care alone (95% CI –0.52 to –7.2). This would translate to 15.6 fewer cluster headache attacks per 4 weeks, or a 23% reduction from baseline. Therefore, we estimated that the cost of productivity loss for nVNS in addition to standard care would be $502.21 per 4 weeks, a decrease of $133.54 in productivity loss per 4 weeks compared to the standard care alone arm. See Appendix 7, Table A17, for details of these calculations.

Model Structure, Migraine

We used a simple Markov model to estimate the costs and QALYs associated with the intervention and comparator. The model has 2 health states: alive (and being treated to prevent migraine), and dead (Figure 8). Patients in the alive state would receive nVNS in addition to standard care (i.e., the new intervention) or standard care alone (i.e., the comparator). Standard care includes other preventive pharmacological treatments for migraine, as well as acute treatment for all people (P. Cooper, MD, email communication, August 2023). Depending on the treatment arm, people in the alive state would incur different costs and utilities (i.e., health-related quality of life), and experience migraine attacks at different frequencies, as observed in the clinical trial. Because the frequency of migraine attacks can vary widely among individuals, we assumed for simplicity that the frequency of migraine attacks (i.e., the number of monthly migraine days) for each treatment arm would be consistent with trial observations. We estimated the utility of the alive state based on the numbers of migraine days and on migraine severity (mild, moderate, and severe). We considered no other events within these states. Patients in the alive state could remain alive or transition to the dead state (due to background or all-cause mortality) every month, which represented the length of a model cycle. We estimated the proportion of people transitioning to the dead state using survival estimates from the 2022 Ontario Life Tables.[92] We assumed no excess mortality due to underlying conditions.

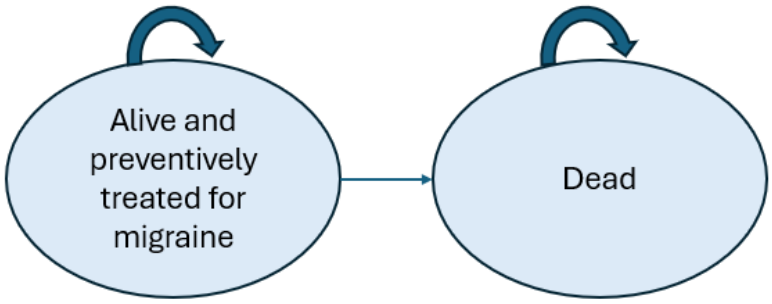

Figure 8: Model Structure, Migraine

The model used for the primary economic evaluation. People in the alive state would receive nVNS in addition to standard care or standard care alone. They could remain alive or transition to the dead state (due to background all-cause mortality) every month, which represented the length of a model cycle.

Clinical Parameters, Migraine

Table 38 summarizes the clinical parameters used in the economic model for migraine.

Table 38: Clinical Parameters Used in the Economic Model, Migraine

Clinical parameter	Mean[a]	Distribution	Reference
Baseline monthly migraine days	8.0 (SE 0.16)	Normal	Average between treatment arms, Diener et al, 2019[57] (PREMIUM)
Mean change in monthly migraine days, standard care	−1.80 (95% CI −2.32 to −1.27)	Normal	Diener et al, 2019[57] (PREMIUM); Table 25 of clinical evidence review
Mean change in monthly migraine days, nVNS in addition to standard care	−2.26 (95% CI −2.81 to −1.72)	Normal	Diener et al, 2019[57] (PREMIUM); Table 25 of clinical evidence review
Baseline number of acute medication days per month	6.9 (SE 0.15)	Normal	Average between treatment arms, Diener et al, 2019[57] (PREMIUM)
Mean change in days of acute medication use, standard care	−1.35 (95% CI −1.91 to −0.79)	Normal	Diener et al, 2019[57] (PREMIUM); Table 29 of clinical evidence review
Mean change in days of acute medication use, nVNS in addition to standard care	−1.9 (95% CI −2.47 to −1.32)	Normal	Diener et al, 2019[57] (PREMIUM); Table 29 of clinical evidence review

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; SE, standard error.

We obtained clinical parameters from the PREMIUM RCT,[57] a double blind, sham-controlled trial that assessed the use of nVNS for prevention in a chronic or episodic migraine population. The primary endpoint of this trial was mean reduction in monthly migraine days. The results showed a mean reduction in monthly migraine days of 2.26 for the nVNS group and 1.80 for the sham group, for a mean difference of 0.46; however, this difference was not statistically significant.

The PREMIUM study also reported a reduction in acute medication days[57]: there was a mean reduction in acute medication days of 1.9 for the nVNS group, and 1.35 for the sham group, for a mean difference of 0.55; however, this difference was not statistically significant.

Treatment-Related Adverse Events

Treatment-related adverse events were the same as for cluster headache (see above).

Utility Parameters, Migraine

We searched for health state utility values associated with nVNS using the same search parameters as described for cluster headache, above.

We identified utility inputs from a 2012 study by Stafford et al,[106] which assessed the health utility scores of 106 people with migraine from the United Kingdom, using EQ-5D (Table 39). We obtained the percentages of people with mild, moderate, and severe migraine (first treated attack severity) from the PRESTO RCT.[84] We used these percentages to calculate the weighted average utility of the alive health state.

Table 39: Utilities Used in the Economic Model, Migraine

Parameter	Mean EQ-5D index score (95% CI) or %	Distribution	Reference
Pain-free	0.87 (0.84 to 0.9)	Beta	Stafford et al, 2012[106]
Mild pain	0.66 (0.62 to 0.71)	Beta	Stafford et al, 2012[106]
Moderate pain	0.53 (0.47 to 0.59)	Beta	Stafford et al, 2012[106]
Severe pain	−0.20 (−0.27 to −0.13)	Beta	Stafford et al, 2012[106]
Proportion with severe migraine	20%	Dirichlet	Tassorelli et al, 2017[84] (PRESTO); weighted average from nVNS and sham arms
Proportion with moderate migraine	44%	Dirichlet	Tassorelli et al, 2017[84] (PRESTO); weighted average from nVNS and sham arms
Proportion with mild migraine	36%	Dirichlet	Tassorelli et al, 2017[84] (PRESTO); weighted average from nVNS and sham arms

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation.

Cost Parameters, Migraine

Cost of the nVNS Device

The cost of the nVNS device for migraine was the same as the cost for cluster headache (Table 36).

Cost of Monitoring, Medication, and Productivity Loss

Table 40 presents the costs of monitoring, medication, and productivity loss for the treatment of migraine in 2023 CAD. We presented the costs as part of standard care from both the Ministry perspective and the societal perspective. Monitoring costs differed between the 2 perspectives because productivity loss and parking costs were included in the societal perspective.

Table 40: Monthly Costs of Monitoring, Medications, and Productivity Loss, Migraine

Migraine cost	Cost per month, Ministry of Health perspective	Cost per month, societal perspective	Reference
Monitoring: neurologist or headache specialist visit	$15.37	$28.12	Schedule of Benefits (A185)[96]
Medication (acute)			
Triptans			
Sumatriptan (all modalities)	$34.05	$141.28	Amoozegar et al, 2022[91]
Almotriptan	$18.59	$77.12	Amoozegar et al, 2022[91]
Rizatriptan	$22.93	$95.14	Amoozegar et al, 2022[91]
Eletriptan[a]	$0.00	$123.72	Amoozegar et al, 2022[91]
Frovatriptan[a]	$0.00	$107.31	Amoozegar et al, 2022[91]
Naratriptan	$22.93	$95.14	Amoozegar et al, 2022[91]
Zolmtriptan	$8.18	$33.94	Amoozegar et al, 2022[91]
Ergots			
Dihydroergotamine[a]	$0.00	$14.98	Amoozegar et al, 2022[91]

Migraine cost	Cost per month, Ministry of Health perspective	Cost per month, societal perspective	Reference
Metoclopramide	$0.01	$0.02	Amoozegar et al, 2022[91]
Ondansetron hydrochloride	$2.89	$12.01	Amoozegar et al, 2022[91]
Opioids			
Analgesics with opioids or barbiturates	$0.56	$2.33	Amoozegar et al, 2022[91]
Medication (prevention)			
Antihypertensives			
Propranolol (40 mg × 2 per d)	$0.90	$3.72	Amoozegar et al, 2022[91]
Nadolol (40 mg)	$3.50	$14.54	Amoozegar et al, 2022[91]
Metoprolol	$0.93	$3.85	Amoozegar et al, 2022[91]
Antidepressants			
Amitriptyline (10 mg)	$0.50	$2.07	Amoozegar et al, 2022[91]
Nortitriptyline[a]	$0.00	$6.89	Amoozegar et al, 2022[91]
Venlafaxine	$0.74	$3.08	Amoozegar et al, 2022[91]
Antiepileptics			
Divalproex dosium/valproic acid	$1.87	$7.75	Amoozegar et al, 2022[91]
Gabapentin	$10.15	$42.11	Amoozegar et al, 2022[91]
Topiramate	$3.17	$13.15	Amoozegar et al, 2022[91]
Calcium channel blockers			
Flunarizine	$1.68	$6.98	Amoozegar et al, 2022[91]
Serotonin antagonists			
Pizotifen	$58.24	$241.66	Amoozegar et al, 2022[91]
Other			
Erenumab	$42.59	$176.71	Amoozegar et al, 2022[91]
Naproxen sodium[a]	$0.00	$3.42	Amoozegar et al, 2022[91]
Diclofenac powder for oral solution[a]	$0.00	$5.89	Amoozegar et al, 2022[91]
Onabotulinum toxin A (botox)	$58.24	$241.66	Amoozegar et al, 2022[91]
Productivity loss (societal perspective only, scenario analysis)	$0	$351.20	Calculated based on Lambert et al[107] and average hourly wage in Ontario[102]

All costs are expressed in 2023 CAD. Medications for which the Ministry of Health costs are $0 indicate that a provincial drug program does not cover the medication. Costs were inflated from 2018 CAD to 2022 CAD in the study by Amoozegar et al.[91] All parameters were modelled as fixed (i.e., no assigned distributions).

[a] This medication is not available for coverage through a public provincial drug program.

Cost of Monitoring and Medication

We assumed that 1 visit per year to a neurologist or headache specialist would be appropriate (P. Cooper, MD, email communication, April 2024), and that a person receiving nVNS in addition to standard care or standard care alone would have the same number of specialist visits. For the societal perspective, we included additional costs, such as time off work to attend doctor's visits and parking costs.

We obtained the costs of migraine medications from a 2018 Canadian (Ontario) burden-of-illness study by Amoozegar et al.[91] The study provided weighted average medication costs from a cohort of 287 people with migraine. This study assumed that people would take preventive migraine medications for 30 days per month, and take acute medications on migraine days (average 14.1 migraine days per month). The study provided annual costs, which we transformed into monthly cost inputs.

To estimate the medication costs from the societal perspective, we added the weighted average costs of all prescription medications included in Amoozegar et al (inflated from 2018 to 2022 CAD).[91] From this perspective, the total monthly cost of acute medication was $673.66 per person, and the total monthly cost of preventive medication was $773.47. From a Ministry of Health perspective, we included only the costs of medications that are covered under the public drug plan and multiplied those costs by 24.1% to represent the proportion of people who are covered by the public drug plan.[103] From a Ministry of Health perspective – multiplying weighted average costs by the proportion of people who are covered by the public drug plan (24.1%) – the total monthly costs of acute and preventive medication were $106.67 and $182.50, respectively.

A clinical expert advised that almost all people use NSAIDs and acetaminophen for the acute treatment of migraine (P. Cooper, MD, email communication, August 2023); however, these medications are available over the counter, so we did not include them in our costing calculations. We did include diclofenac because this NSAID requires a prescription.

Based on the PREMIUM RCT,[57] we estimated that people receiving nVNS in addition to standard care would have a reduction in the use of acute medication. Over both arms of the study, patients experienced a reduction in the number of acute medication use days of 0.55 days per month: for nVNS in addition to standard care, an average reduction of 1.9 days per month (95% CI −2.47 to −1.32) and for standard care alone, an average reduction of 1.35 days per month (95% CI −1.91 to −0.79).

We calculated a daily average cost for acute medication based on Amoozegar et al[91] and estimated that people receiving nVNS would experience a reduction of $14.38 in costs for acute medication use per month from a Ministry of Health Perspective, and a reduction of $90.78 in costs for acute medication use per month from a societal perspective.

Migraine Cost of Productivity Loss (Scenario)

In a scenario analysis, we considered the costs of productivity loss due to migraine from a societal perspective. A Canadian study by Lambert et al[107] administered a Migraine Background Questionnaire during the phase III stage of a clinical trial assessing the use of rizatriptan in people with migraine. The authors found that among the 143 people with migraine who completed the questionnaire, the average person reported 6.5 days of absenteeism from work and 10.4 days of presenteeism. We calculated the estimated cost of productivity loss due to migraine by multiplying 16.9 days per year (absenteeism and presenteeism) by the average hourly pay rate in Ontario ($33.25 CAD per hour).[102] The cost of productivity loss was approximately $4,214.44 per year or $351.20 per month for people receiving standard care only.

For people receiving nVNS in addition to standard care, we estimated that there would be a small decrease in the costs of productivity loss. We based this estimate on a decrease in baseline monthly migraine days. According to the PREMIUM RCT,[53] people receiving nVNS in addition to standard care experienced a reduction of 2.26 (95% CI −2.81 to −1.72) migraine days per month compared to those

receiving standard care alone, who experienced a reduction of 1.80 (95% CI −2.32 to −1.27) migraine days per month, for a difference of 0.46 fewer migraine days per month in the nVNS arm. The baseline number of average migraine days per month for both arms was 8.0 days. Therefore, the estimated cost of productivity loss for nVNS in addition to standard care arm was $295.19 per month. See Appendix 7, Table A18, for details of these calculations.

Internal Validation

The secondary health economist conducted formal internal validation. This process included reviewing and providing feedback on the model design, project plan and final draft report; testing the mathematical logic of the model; checking for errors; and ensuring the accuracy of parameter inputs and equations.

Analysis

Our reference case and sensitivity analyses adhered to the Canadian Agency for Drugs and Technologies in Health guidelines when appropriate.[86] The reference case represents the analysis with the most likely set of input parameters and model assumptions.

We calculated the reference case analysis by running 5,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters that were expected to vary. We set distributions for variables within the model. We calculated mean costs with credible intervals and mean QALYs with credible intervals for each intervention assessed. We also calculated the mean incremental costs with credible intervals, incremental QALYs with credible intervals, and ICERs for nVNS in addition to standard care versus standard care alone.

The results of the probabilistic analysis are presented in a scatter plot on a cost-effectiveness plane and in a cost-effectiveness acceptability curve. Although not used as definitive willingness-to-pay (WTP) thresholds, including graphical indications of the location of the results relative to commonly used WTP values of $50,000 per QALY and $100,000 per QALY facilitates interpretation of the findings and comparison with historical decisions. We also present uncertainty quantitatively as the probability that an intervention is cost-effective at previously mentioned WTP guideposts. This uncertainty is also presented qualitatively, in 1 of 5 categories defined by the Ontario Decision Framework[108]: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely to not be cost-effective (20%–39% probability), or highly likely to not be cost-effective (0%–19% probability).

Scenario Analyses

The scenario analyses we conducted (for both disease areas) are described below and in Table 41:

- Scenario 1 – cost of the nVNS device, plus or minus 25% (± $1,594 of the annual cost).
- Scenario 2 – societal perspective: this scenario considered the costs incurred from a societal perspective. Not all people are covered under a public drug plan, and some people would pay out of pocket or be covered by private insurance. In this scenario, we included drug costs at a rate of 100% (capturing out-of-pocket drug expenses, publicly paid drug expenses, and private coverage). As well,

because much of the population for cluster headache and migraine were assumed to be of working age, we included costs associated with lost productivity.

- Scenario 3 – the nVNS device is provided free for the first 93 days. This scenario is based on the pricing scheme available in the United Kingdom, where gammaCore was provided at no cost for the initial 3-month trial. In the reference case, the full annual cost of the device ($6,376) is included over 1 year; in this scenario, the initial prescription ($2,206) is excluded, resulting in an annual cost of $4,170.
- Scenario 4 – change in the clinical pathway. In the reference case, we assumed that prescribing of the nVNS device would be limited to headache specialists or neurologists. In this scenario, we assumed that a general practitioner could prescribe the device and see the person for follow-up visits. In this scenario, we also assumed that people receiving standard care would also be seen by a general practitioner.
- Scenario 5 – change in time horizon. For these analyses, we used 6-month and 2-year time horizons (discounting by 1.5% for costs and outcomes in the 2-year scenario).
- Scenario 6 – assumption regarding long-term health utility benefit in the intervention arm (cluster headache model only). In this scenario, instead of using a constant rate of utility benefit (assumed to be 100% in the reference case), we decreased the utility benefits in the nVNS arm by 25% (75% of full utility benefits were experienced in this scenario).
- Scenario 7 – response-dependent treatment continuation. In this scenario, we assumed that only responders according to the PREVA RCT[53] definition of response for cluster headache (proportion of people who experienced a reduction of 50% or greater in the mean number of cluster headache attacks per week) and the PREMIUM RCT[57] definition for migraine (proportion of people who experienced a reduction of 50% or greater in migraine days from baseline to the last 4 weeks of randomization) would continue to use nVNS over the long term (i.e., after 3 months), and they would experience benefits similar to what was observed in the clinical trials. We assumed that nonresponders would discontinue nVNS treatment, and their clinical outcomes would be the same as people receiving standard care alone.
- Scenario 8 – threshold analysis for the reduction of acute medication use in people with cluster headache (cluster headache model only). We used this scenario to identify the threshold value at which the reduction in acute medication use with nVNS would no longer be cost-effective for people with cluster headache.
- Scenario 9 – nasal sumatriptan spray to replace sumatriptan injections as acute treatment (cluster headache model only). In this scenario, we replaced the sumatriptan injections (acute medication in the reference case) with sumatriptan nasal spray. We did not include sumatriptan nasal spray in the reference case because public coverage for this drug is provided by the exceptional access program.
- Scenario 10 – publicly available Canadian costs for nVNS device used. In this scenario, we replaced the manufacturer-provided costs of nVNS with those that are publicly listed on the gammaCore prescription form for prescribers ($650 initial 93-day prescription, $650 subsequent 93-day prescriptions).

Table 41: Variables Varied in Scenario Analyses: Cluster Headache and Migraine

Scenario	Model applicability	Reference case	Scenario analysis
1: Cost of the nVNS device	Cluster headache and migraine	$6,376 CAD/y	± 25% ($1,594) cost variation
2: Societal perspective	Cluster headache and migraine	Ministry of Health perspective	Including health care-related out-of-pocket expenses for patients, as well as costs of productivity loss
3: nVNS provided free for the first 93 days	Cluster headache and migraine	No free trial	Free trial for the first 93 d
4: Change in the clinical pathway	Cluster headache and migraine	Assume that neurologists or headache specialists prescribe nVNS and guide patient care	Assume general practitioners prescribe nVNS and guide patient care
5: Change in time horizon	Cluster headache and migraine	1 y	6 mo and 2 y
6: Changes in quality of life in the nVNS arm for people with cluster headache	Cluster headache	Patients experience 100% constant utility benefits throughout the model time horizon	Beyond 12 wk, utility benefits decrease to 75%
7: Response-dependent treatment continuation beyond 3 mo	Cluster headache and migraine	Patients continue to use nVNS after the trial period and experience the same average effects as observed in the clinical trials	Nonresponders stop receiving nVNS after 3 mo, and the costs and effectiveness are assumed to be the same between arms beyond 3 mo
8: Reduction in acute medication use in people with cluster headache	Cluster headache	61% reduction in the use of subcutaneous sumatriptan injections with nVNS	0% reduction in the use of acute medication with nVNS and standard care
9: Nasal sumatriptan spray to replace sumatriptan injections in people with cluster headache	Cluster headache	Sumatriptan injections used for acute treatment of cluster headache	Nasal sumatriptan spray replaces sumatriptan injection
10: Publicly available Canadian costs for nVNS device used	Cluster headache and migraine	Using manufacturer-provided costs for nVNS device used	$650 initial 93 d prescription, $650 subsequent 93 d prescriptions[109]

All costs expressed in 2023 CAD.

Abbreviations: nVNS, noninvasive vagus nerve stimulation.

Results

Cluster Headache

Reference Case Analysis

Tables 42a and b provides the results of the reference case analysis for cluster headache, from a Ministry of Health perspective. The mean total cost for nVNS in addition to standard care was $7,833, and the mean total cost for standard care alone was $2,516. The up-front cost of the nVNS device was high ($6,369), but this was partially offset by savings (−$1,052) from reduced use of acute medications (i.e., sumatriptan injections). The mean total effect was 0.6941 QALYs for nVNS in addition to standard care and 0.4996 QALYs for standard care alone, resulting in an increase of 0.1945 QALYs. Treatment with nVNS in addition to standard care compared with standard care alone resulted in an ICER of $27,338 per QALY over 1 year. We also conducted a cost-effectiveness analysis and found that nVNS use reduced the average number of annual cluster headache attacks by 201. This translated to a cost of $26.40 per cluster headache attack avoided.

Table 42a: Reference Case Analysis, Disaggregated Results, Cluster Headache

Outcome	nVNS in addition to standard care, mean (95% CrI)	Standard care alone, mean (95%CrI)	Mean difference (95% CrI)[a,b]
Cost outcomes			
Total cost per person per year	$7,833 ($7,549 to $8,267)	$2,516 ($1,975 to $3,070)	$5,317 ($4,859 to $5,728)
Cost of nVNS	$6,369	$0	$6,369
Cost of acute medication	$668	$1,720	−$1,052
Cost of preventive medication	$599	$599	$0
Cost of monitoring	$1,116	$1,116	$0
Effectiveness outcomes			
Number of attacks per year	671 (433 to 908)	872 (712 to 1,030)	−201 (−378 to −21)
Total QALYs	0.6941 (0.4642 to 0.8931)	0.4996 (0.3140 to 0.6411)	0.1945 (0.0461 to 0.3276)

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; nVNS; noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.

[a] Results may appear inexact due to rounding.

[b] Negative costs indicate savings.

Table 42b: Reference Case Analysis Results, Cluster Headache

Strategy	Average total costs, $ (95% CrI)	Incremental cost, $ (95% CrI)[a,b]	Average total effect, QALYs (95% CrI)	Incremental effect, QALYs (95% CrI)[b,c]	ICER, $/QALY[c]
Standard care alone	2,516 (1,975 to 3,070)	–	0.4996 (0.3140 to 0.6411)	–	–
nVNS in addition to standard care	7,833 (7,549 to 8,267)	5,317 (4,859 to 5,728)	0.6941 (0.4642 to 0.8931)	0.1945 (0.0461 to 0.3276)	27,338

Abbreviations: ICER, incremental cost-effectiveness ratio; nVNS; noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.

[a] Incremental cost = average cost (nVNS with standard care) − average cost (standard care alone).

[b] Results may appear inexact due to rounding.

[c] Incremental effect = average effect (nVNS with standard care) − average effect (standard care alone).

The results of our probabilistic analysis are presented in a cost-effectiveness acceptability curve (Figure 9) and as a scatter plot on a cost-effectiveness plane (Figure 10). The results of this analysis show that at the commonly used WTP values of $50,000 and $100,000 per QALY, the probabilities of nVNS in addition to standard care being cost-effective were 88.5% and 97%, respectively. This means that nVNS in addition to standard care is highly likely to be cost-effective.

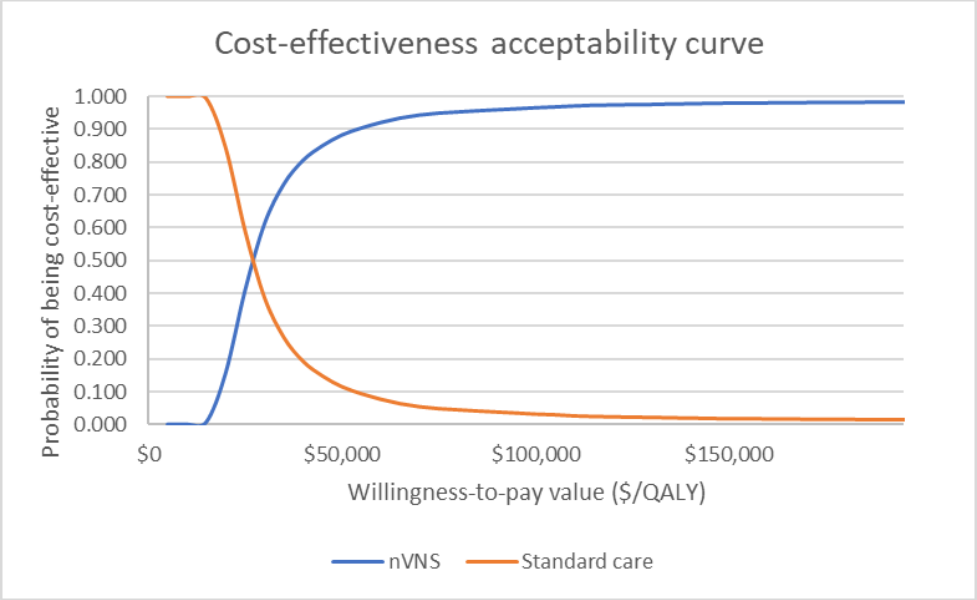

Figure 9: Cost-Effectiveness Acceptability Curve, Cluster Headache

A cost-effectiveness acceptability curve showing the results of the probabilistic analysis. nVNS in addition to standard care was highly likely to be cost-effective at WTP values of $50,000, $100,000, and $150,000.

Abbreviations: nVNS, noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.

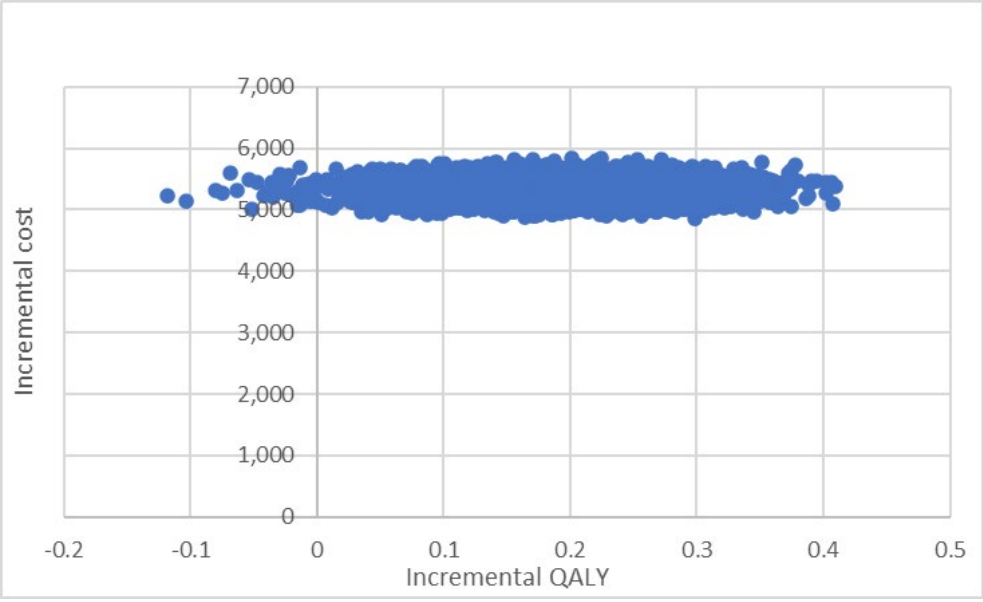

Figure 10: Scatter Plot of Probabilistic Results, Cluster Headache

A scatterplot of probabilistic results showing the findings from the 5,000 model iterations. The incremental cost is approximately $5,000 and the incremental QALY ranged from –0.1 to 0.4.

Abbreviations: QALY, quality-adjusted life-year.

Scenario Analysis

Our scenario analyses showed that results generally remained robust and did not deviate substantially from the reference case results. As well, all scenarios yielded ICERs below $50,000 per QALY gained, (i.e., nVNS was cost effective at a WTP value of $50,000 in all scenarios; see Table 43). The ICER changed most when the nVNS device costs reflected costs from publicly available price lists, which were lower than the costs used in the reference case ($2,600 per year vs. $6,369 per year).

Four scenarios yielded ICERs that were lower than the reference case ICER: scenario 1a (cost of the nVNS device reduced by 25%), scenario 3 (nVNS device provided free for the first 93 days), scenario 5b (time horizon extended to 2 years), and scenario 10 (publicly available Canadian costs for nVNS device used).

Four scenarios yielded ICERs that were higher than the reference case ICER: scenario 1b (cost of the nVNS device increased by 25%), scenario 6 (changes in quality of life in the nVNS arm), scenario 8 (0% reduction in acute medication use), and scenario 9 (sumatriptan nasal spray to replace sumatriptan injections).

Three scenarios affected the ICER only minimally (difference of < $500 per QALY gained between the reference case and the scenario: scenario 4 (change in the clinical pathway), scenario 5a (time horizon reduced to 6 months), and scenario 7 (response-dependent treatment continuation).

Table 43: Scenario Analysis Results, Cluster Headache

Strategy	Average total cost, $	Incremental cost, $[a,b]	Average total effect, QALYs	Incremental effect, QALYs[b,c]	ICER, $/QALY[b]
Reference case	Standard care: 2,516 nVNS: 7,833	5,317	Standard care: 0.4996 nVNS: 0.6941	0.1945	27,338
1a: Cost of the nVNS device reduced by 25%	Standard care: 2,508 nVNS: 6,241	3,733	Standard care: 0.4977 nVNS: 0.6894	0.1918	19,470
1b: Cost of the nVNS device increased by 25%	Standard care: 2,513 nVNS: 9,424	6,910	Standard care: 0.4987 nVNS: 0.6910	0.1924	35,925
3: nVNS provided free for the first 93 d	Standard care: 2,512 nVNS: 5,631	3,119	Standard care: 0.4977 nVNS: 0.6904	0.1927	16,187
4: Change in the clinical pathway	Standard care: 2,415 nVNS: 7,737	5,321	Standard care: 0.4959 nVNS: 0.6900	0.1940	27,424
5a: Time horizon reduced to 6 mo	Standard care: 1,163 nVNS: 3,620	2,457	Standard care: 0.2306 nVNS: 0.3203	0.0897	27,397
5b: Time horizon extended to 2 y (1.5% discount on costs and effects)	Standard care: 4,984 nVNS: 14,741	9,757	Standard care: 0.9879 nVNS: 1.372	0.3848	25,356
6: Changes in quality of life in the nVNS arm for people with cluster headache	Standard care: 2,513 nVNS: 7,838	5,325	Standard care: 0.4977 nVNS: 0.6655	0.1578	33,738
7: Response-dependent treatment continuation beyond 3 mo (60% nonresponder rate, Gaul 2015[53])[d]	Standard care: 2,514 nVNS: 5,376	2,862	Standard care: 0.4990 nVNS: 0.6040	0.1050	27,267
8: Reduction in acute medication use by people with cluster headache (assuming 0% reduction)	Standard care: 2,512 nVNS: 8,882	6,369	Standard care: 0.4985 nVNS: 0.6923	0.1938	32,866
9: Sumatriptan nasal spray to replace sumatriptan injections in people with cluster headache	Standard care: 1,640 nVNS: 8,010	6,369	Standard care: 0.4969 nVNS: 0.6896	0.1927	33,061
10: Publicly available Canadian costs for nVNS device used	Standard care: 2,512 nVNS: 4,063	1,552	Standard care: 0.4981 nVNS: 0.6927	0.1946	7,973

All costs are expressed in 2023 CAD.

Abbreviations: ICER, incremental cost-effectiveness ratio; nVNS, noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.

[a] Incremental cost = average cost (nVNS with standard care) − average cost (standard care alone).

[b] Results may appear inexact due to rounding. Changes in effectiveness outcomes (QALYs) may be present when scenarios address only costs, due to the probabilistic nature of our model.

[c] Incremental effect = (nVNS with standard care) − average effect (standard care alone).

[d] Nonresponder rates were calculated as 1 – the responder rate identified in the randomized, controlled trial.

The cost–utility analysis for the use of nVNS to prevent cluster headache from a societal perspective showed that the mean total cost for nVNS in addition to standard care was $21,651, and the mean total cost for standard care alone was $26,506 (Table 44). nVNS in addition to standard care had lower overall costs (by $4,855) largely due to a reduction in acute medication use of very expensive medications (e.g., inhaled oxygen is not covered by the Ministry of Health), as well as a reduction in

productivity loss. Incremental QALYs for the societal perspective (0.1943) were very similar to those reported in the reference case. The ICER showed that nVNS in addition to standard care was a dominant strategy (i.e., more effective and less costly than standard care alone).

Table 44: Scenario Analysis Results, Societal Perspective, Cluster Headache

Strategy	Average total cost, $ (95% CrI)	Incremental cost, $ (95% CrI)[a,b,c]	Average total effect, QALYs (95% CrI)	Incremental effect, QALYs (95% CrI)[c,d]	ICER, $/QALY[c]
Standard care alone	26,506 (22,284 to 30,538)	–	0.5000 (0.3203 to 0.6369)	–	–
nVNS in addition to standard care	21,651 (18,129 to 25,362)	−4,855 (−8,346 to −1,687)	0.6943 (0.4728 to 0.8866)	0.1943 (0.0498 to 0.3232)	Dominant

Abbreviations: CrI, Credible confidence interval; ICER, incremental cost-effectiveness ratio; nVNS, noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.

[a] Incremental cost = average cost (nVNS with standard care) − average cost (standard care alone).

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

[d] Incremental effect = average effect (nVNS with standard care) − average effect (standard care alone).

Migraine

Reference Case Analysis

Table 45 provides the results of the reference case analysis results for migraine from a Ministry of Health perspective. The mean total cost for nVNS in addition to standard care was $9,200, and the mean total cost for standard care alone was $2,877. The upfront cost of the nVNS device was high ($6,372), and the savings from reduced use of acute medication was relatively small (−$48). The mean total effect was 0.7876 QALYs for nVNS in addition to standard care and 0.7809 QALYs for standard care alone, resulting in minimal change in QALYs (an increase of 0.0066 QALYs). Treatment with nVNS in addition to standard care compared with standard care alone resulted in an ICER of $952,116 per QALY over 1 year. We also conducted a cost-effectiveness analysis and found that nVNS use reduced the average number of monthly migraine days by 5.6 days per year. This translates to a cost of $1,129 per migraine day avoided.

Table 45a: Reference Case Analysis Disaggregated Results, Migraine

Outcome	nVNS in addition to standard care, mean (95% CrI)	Standard care alone, mean (95%CrI)	Mean difference (95% CrI)[a,b]
Cost outcomes			
Total cost per person per year	$9,200 ($8,892 to $9,507)	$2,877 ($2,818 to $2,934)	$6,324 ($6,016 to $6,642)[a]
Cost of nVNS	$6,372	$0	$6,372
Cost of acute medication	$456	$504	−$48[b]
Cost of preventive medication	$2,189	$2,189	$0
Cost of monitoring	$184	$184	$0
Effectiveness outcomes			
Number of migraine days per year	69.84 (61 to 76)	74.44 (67 to 81)	−5.60[d]
Total QALYs	0.7876 (0.7595 to 0.8144)	0.7809 (0.7533 to 0.8076)	0.0066 (−0.0053 to 0.0186)[d]

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; nVNS; noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.
[a] Results may appear inexact due to rounding.
[b] Negative costs indicate savings.

Table 45b: Reference Case Analysis Results, Migraine

Strategy	Average total cost, $ (95% CrI)	Incremental cost, $ (95% CrI)[a,b]	Average total effect, QALYs (95% CrI)	Incremental effect, QALYs (95% CrI)[b,c]	ICER, $/QALY[c]
Standard care alone	2,877 (2,818 to 2,934)	–	0.7809 (0.7533 to 0.8076)	–	–
nVNS in addition to standard care	9,200 (8,892 to 9,507)	6,324 (6,016 to 6,642)	0.7876 (0.7595 to 0.8144)	0.0066 (−0.0053 to 0.0186)	952,116

Abbreviations: ICER, incremental cost-effectiveness ratio; nVNS; noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.
[a] Incremental cost = average cost (nVNS with standard care) − average cost (standard care alone).
[b] Results may appear inexact due to rounding.
[c] Incremental effect = average effect (nVNS with standard care) − average effect (standard care alone).

The results of our probabilistic analysis are presented in a cost-effectiveness acceptability curve (Figure 11) and as a scatter plot on a cost-effectiveness plane (Figure 12). The results of this analysis show that at the commonly used WTP values of $50,000 and $100,000 per QALY, the probability of nVNS in addition to standard care being cost-effective was 0.00% and 0.00%, respectively. At a WTP of $150,000 per QALY, the probability of nVNS being cost-effective was also 0.00%. This means that nVNS in addition to standard care is highly unlikely to be cost-effective, and the likelihood of it being cost-effective did not increase as the WTP increased.

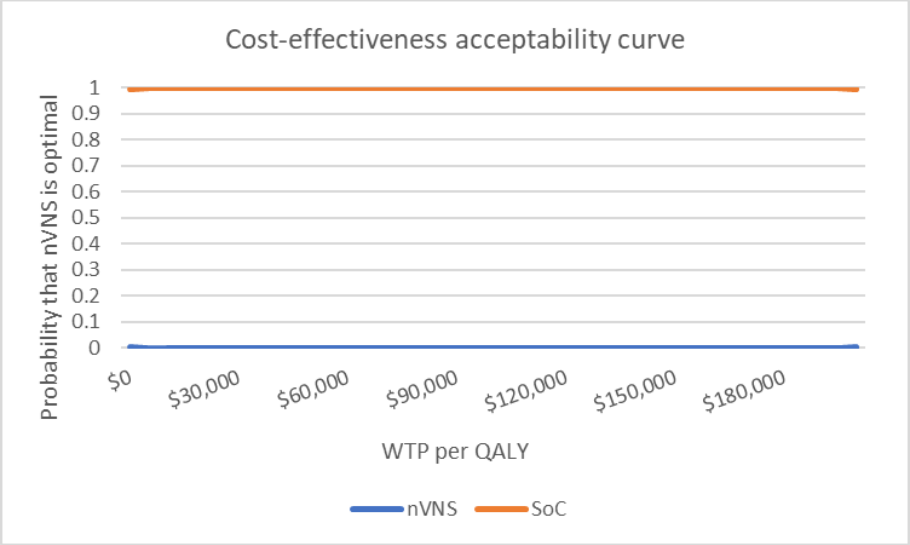

Figure 11: Cost-Effectiveness Acceptability Curve, Migraine

A cost-effectiveness acceptability curve showing the results of the probabilistic analysis. nVNS in addition to standard care was highly unlikely to be cost-effective at any WTP value.

Abbreviations: nVNS, noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year; SoC, standard of care; WTP, willingness to pay.

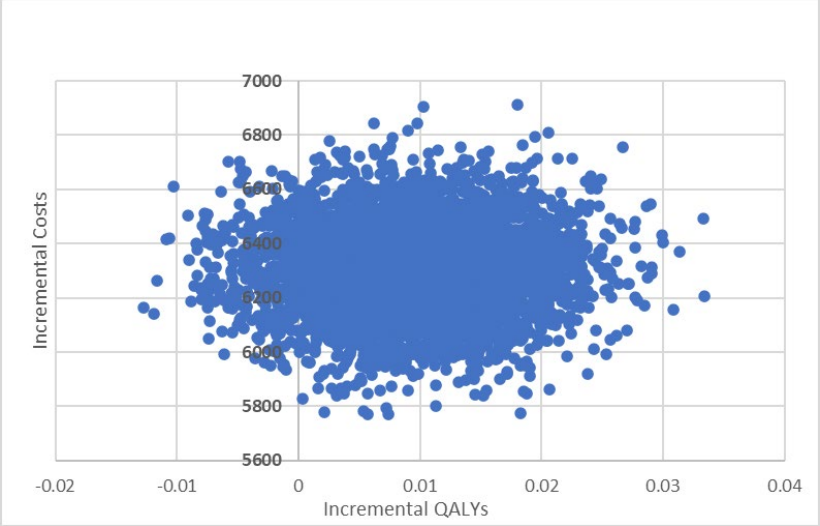

Figure 12: Scatter Plot of Probabilistic Results, Migraine

A scatter plot of probabilistic results showing the findings from the 5,000 model iterations. There were large increments in costs and very small or no increments in QALYs, resulting in a lack of cost-effectiveness for nVNS vs. standard care at commonly used WTP values.

Abbreviations: QALY, quality-adjusted life-year; WTP, willingness to pay.

Scenario Analysis

None of the scenario analyses showed that nVNS was cost-effective at a WTP value of $150,000 per QALY gained (Table 46). In general, the results remained robust and did not deviate substantially from the reference case results. The ICER was most sensitive when we assumed that nVNS treatment would be discontinued beyond 3 months for those who did not initially respond to the treatment (i.e., scenario 7).

Four scenarios yielded ICERs that were lower than the reference case ICER: scenario 1 (nVNS device costs reduced by 25%), scenario 3 (nVNS device offered at no cost to the Ministry of Health for 93 days, scenario 5b (time horizon extended to 2 years), and scenario 10 (reduced Canadian nVNS costs).

Three scenarios yielded ICERs that were higher than the reference case ICER: scenario 1b (nVNS device costs increased by 25%), scenario 4 (change in clinical pathway, general practitioner visit instead of neurologist visit), and scenario 5a (time horizon reduced to 6 months).

One scenario yielded an ICER for which nVNS was dominated: scenario 7 (response-dependent treatment continuation beyond 3 months).

Table 46: Scenario Analysis Results, Migraine

Analysis	Average total cost, $	Incremental cost, $[a,b]	Average total effect, QALYs	Incremental effect, QALYs[b,c]	ICER, $/QALY[b]
Reference case	Standard care: 2,877 nVNS: 9,200	6,324	Standard care: 0.7809 nVNS: 0.7876	0.0066	952,116
1a: Cost of the nVNS device reduced by 25%	Standard care: 2,876 nVNS: 7,605	4,730	Standard care: 0.7811 nVNS: 0.7876	0.0065	724,482
1b: Cost of the nVNS device increased by 25%	Standard care: 2,876 nVNS: 10,792	7,916	Standard care: 0.7809 nVNS: 0.7873	0.0064	1,239,586
3: nVNS provided free for the first 93 d	Standard care: 2,876 nVNS: 6,989	4,113	Standard care: 0.7806 nVNS: 0.7871	0.0065	634,211
4: Change in the clinical pathway	Standard care: 2,779 nVNS: 9,105	6,326	Standard care: 0.7813 nVNS: 0.7878	0.0066	965,211
5a: Time horizon reduced to 6 mo	Standard care: 1,439 nVNS: 4,600	3,162	Standard care: 0.3907 nVNS: 0.3939	0.0032	979,467
5b: Time horizon extended to 2 y (1.5% discount on costs and effects	Standard care: 5,706 nVNS: 17,438	11,732	Standard care: 1.5649 nVNS:1.5623	0.0129	911,669
7: Response-dependent treatment continuation beyond 3 mo (68.1% nonresponder rate, Diener, 2019[57])[d]	Standard care: 2,876 nVNS: 6,031	3,154	Standard care: 0.7807 nVNS: 0.7708	−0.0099	nVNS was dominated (i.e., more costly and less effective)
10: Publicly available Canadian costs for nVNS device used	Standard care: 2,867 nVNS: 5,424	2,547	Standard care: 0.7814 nVNS: 0.7877	0.0064	398,756

All costs are expressed in 2023 CAD.

Abbreviations: ICER, incremental cost-effectiveness ratio; nVNS, noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.

[a] Incremental cost = average cost (nVNS with standard care) − average cost (standard care alone).

[b] Results may appear inexact due to rounding. Changes in effectiveness outcomes (QALYs) may be present when scenarios address only costs, due to the probabilistic nature of our model.

[c] Incremental effect = average effect (nVNS with standard care) − average effect (standard care alone).

[d] Nonresponder rates were calculated as 1 – the responder rate identified in the randomized, controlled trial.

The cost–utility analysis for the use of nVNS to treat migraine from a societal perspective showed that the mean total cost for nVNS in addition to standard care was $21,873, and the mean total cost for standard care alone was $16,058 (Table 47). nVNS in addition to standard care had higher overall costs (by $5,815) because of the cost of the nVNS device. Incremental QALYs from a societal perspective were identical to those reported in the reference case. Treatment with nVNS in addition to standard care compared with standard care alone resulted in an ICER of $878,376 per QALY.

Table 47: Scenario Analysis Results, Societal Perspective, Migraine

Strategy	Average total cost, $ (95% CrI)	Incremental cost, $ (95% CrI)[a,b]	Average total effect, QALYs (95% CrI)	Incremental effect, QALYs (95% CrI)[b,c]	ICER, $/QALY[b]
Standard care alone	16,058 (15,787 to 17,989)	–	0.7805 (0.7522 to 0.8070)	–	–
nVNS in addition to standard care	21,873 (19,798 to 24,018)	5,815 (3,831 to 7,802)	0.7871 (0.7584 to 0.8141)	0.0066 (−0.0049 to 0.0182)	878,376

Abbreviations: CrI, Credible confidence interval; ICER, incremental cost-effectiveness ratio; nVNS; noninvasive vagus nerve stimulation; QALY, quality-adjusted life-year.

[a] Incremental cost = average cost (nVNS with standard care) − average cost (standard care alone).

[b] Results may appear inexact due to rounding.

[c] Incremental effect = average effect (nVNS with standard care) − average effect (standard care alone).

Discussion

Cluster Headache

Our reference case results showed that nVNS in addition to standard care for the prevention of cluster headache is likely to be cost-effective. The cost of the nVNS device ($6,369 per person per year) was partially offset by savings associated with the reduction of acute medication use (–$1,052 per person per year). This was consistent with the findings of other published economic studies,[65,81,82] which also suggested that nVNS may lead to cost savings due to the reduced use of acute medication. However, our results should be interpreted with caution. Although our economic evaluations provide valuable insights, the clinical inputs that informed our modelling were of Low to Very low quality according to GRADE assessment. As well, long-term data on the use of nVNS treatment are lacking, so the long-term benefits of nVNS are uncertain.

When we conducted a scenario analysis from a societal perspective, nVNS in addition to standard care was dominant (i.e., less costly and more effective). This is because of increased savings associated with reduced acute medication use (some of the acute treatments, such as inhaled oxygen, are not covered by the public drug plan) and savings resulting from potential improvements in productivity.

Migraine

Our reference case results showed that nVNS in addition to standard care for the prevention of migraine is highly unlikely to be cost-effective at commonly used WTP values of $50,000 and $100,000 per QALY gained. The ICERs remained consistently above $300,000 per QALY gained in all sensitivity and scenario analyses. In other words, the additional costs incurred with the addition of nVNS would not justify the change in health outcomes measured in QALYs. Our results suggested a minimal difference in QALYs for nVNS in addition to standard care compared with standard care alone.

This finding was different from that of cluster headache, where nVNS was cost-effective due to a combination of factors, including a greater reduction in acute medication costs and improvements in quality of life (as observed in the PREVA trial[53]). However, in the context of migraine, the reduction in acute medication costs associated with nVNS use was minimal (a decrease of $48 per person per year).

No data were identified for adolescents. An expert advised that adolescents who choose not to take medication for migraine may consider nVNS as a treatment option (M. Lagman, MD, email consultation, May 2023).

Equity Considerations

By conducting a scenario analysis from a societal perspective, we captured the costs of standard care that are borne by patients and are not captured from the perspective of the Ministry of Health. Out-of-pocket expenses for people with cluster headache and migraine were substantial and were reflected in this scenario analysis.

Publicly funding nVNS may improve access to an effective treatment for people who cannot afford the out-of-pocket costs or who do not have private insurance coverage. Funding this technology could also reduce inequity as a result of improved access to treatment for people who live in remote areas and require treatment at a physician's office (e.g., nerve block injections, botulinum toxin type A injections) or regular drug monitoring.

Strengths and Limitations

A strength of our analysis is that we conducted it from both a Ministry of Health perspective and a societal perspective. Not all components of standard care for cluster headache and migraine are covered under a provincial public drug program, so consideration of a societal perspective provided a meaningful context for the amounts and types of costs incurred by people with cluster headache and migraine. To ensure that our results were generalizable to the context of health care in Ontario and Canada, we derived our cost parameters largely from local sources, including the Ontario Schedule of Benefits,[96] the publicly available Ontario Drug Benefit formulary,[99] and an Ontario burden-of-illness study[91] (from which we derived weighted average costs for migraine medication use).

Some limitations of our analysis should be noted. First, we were unable to conduct analyses for cluster headache and migraine with a focus on nVNS for acute treatment because of a lack of available utility data and the difficulty associated with translating acute effectiveness outcomes (such as achieving pain-free status within 15 minutes after treatment initiation) into QALYs. Second, because only 1 nVNS device currently has Health Canada approval, the evidence we used to generate our economic model for a class of nVNS devices was based on information about a single device (gammaCore from electroCore). Third, the long-term effectiveness of nVNS use is uncertain because current RCTs have short follow-up periods. Our model time horizon of 1 year reflected these limitations, but it may not fully capture the potential benefits of nVNS for cluster headache and migraine. Fourth, our scenario analysis from a societal perspective did not capture potential costs of caregiving for those with cluster headache and migraine, resulting in a potential underestimate of the full societal costs associated with these conditions. There is also limited information available on productivity loss related to cluster headache in Canada; we estimated the costs of productivity loss based on a US study. Last, in our economic models for cluster headache and migraine we did not capture the potential decline in treatment-related adverse events associated with a reduction in acute medication use associated with nVNS. This is notable, because we

anticipate that a reduction in the number of sumatriptan succinate injections – and an associated reduction in anticipated treatment-related adverse events – could improve quality-of-life outcomes and reduce the costs of addressing adverse events related to standard care. For this reason, our analysis may provide more conservative estimates of quality-of-life improvements and cost savings.

Conclusions

For the prevention of cluster headache, nVNS in addition to standard care (compared with standard care alone) was associated with an additional 0.1945 QALYs and an additional cost of $5,317 per person, resulting in an ICER of $27,338 per QALY gained over a 1-year time horizon. In general, our scenario analyses illustrated the robustness of these results and the cost-effectiveness of nVNS for the prevention of cluster headache. The results of our probabilistic analysis showed that at the commonly used WTP values of $50,000 and $100,000 per QALY gained, the probabilities of nVNS in addition to standard care being cost-effective were 88.5% and 97%, respectively. At a WTP of $150,000 per QALY gained, the probability of the nVNS strategy being cost-effective was 98.12%. This means that nVNS in addition to standard care is highly likely to be cost-effective compared to standard care alone.

For the prevention of migraine, nVNS in addition to standard care (compared with standard care alone) was associated with minimal change in QALYs and an additional cost of $6,324, resulting in an ICER of $952,116 per QALY gained over a 1-year time horizon. The results of our probabilistic analysis showed that at commonly used WTP values of $50,000 and $100,000 per QALY gained, the probabilities of nVNS in addition to standard care being cost-effective were 0.00% and 0.00%, respectively. At a WTP of $150,000 per QALY gained, the probability of the nVNS strategy being cost-effective remained 0.00%. This means that nVNS in addition to standard care is highly unlikely to be cost-effective, and the likelihood of it being cost-effective did not increase as the WTP increased.

Our cost-effectiveness findings for cluster headache and migraine should be interpreted with caution because of the low quality of the clinical inputs used to inform our modelling. The cost-effectiveness of nVNS for the acute treatment of both conditions in Ontario is unknown.

Budget Impact Analysis

Research Questions

- What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding noninvasive vagus nerve stimulation (nVNS) in addition to standard care for the acute treatment or prevention of cluster headache in adults?
- What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding nVNS in addition to standard care for the acute treatment or prevention of migraine in adults and adolescents?

Methods

Analytic Framework

We estimated the budget impact of publicly funding nVNS using the cost difference between 2 scenarios: (1) current clinical practice without public funding for nVNS (the current scenario) and (2) anticipated clinical practice with public funding for nVNS (the new scenario). Figure 13 presents the model schematic.

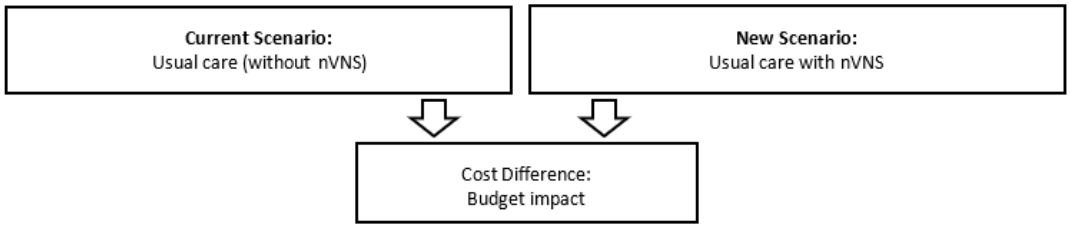

Figure 13: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. The current scenario would explore resource use and total costs without public funding for nVNS. The new scenario would explore resource use and total costs with public funding for nVNS. The budget impact would represent the difference in costs between the 2 scenarios.
Abbreviation: nVNS, noninvasive vagus nerve stimulation.

Key Assumptions

- The prevalence of cluster headache and migraine would remain stable over the next 5 years.
- The cost of nVNS would stay constant over the next 5 years. The market price of nVNS includes startup and implementation costs (e.g., training and credentialling), and these costs were not considered separately.
- Standard care and its costs for cluster headache or migraine would stay constant over the next 5 years.
- Uptake rates of nVNS for cluster headache and migraine would be the same. We provided separate budget impact estimates for these populations and tested this assumption in a scenario analysis.

Population of Interest

Tables 48 and 49 show the estimates for the population of interest for cluster headache and migraine. We obtained the total Ontario population figure from the Ministry of Finance population projections for 2022 to 2046.[110] We based year 1 calculations on the 2024 population, and year 5 calculations on the 2028 population.

Cluster Headache

Information about the prevalence of cluster headache in Canada is limited; however, combined global population-based studies have estimated that 0.1% of the population has cluster headaches.[6] An expert advised us that cluster headache presents in adults and rarely in adolescents (M. Lagman, MD, oral and email communication, May 2023), so we considered only the adult population for this analysis. An expert also advised us that approximately 90% of people with cluster headache are eligible for nVNS treatment (i.e., nVNS is not contraindicated; M. Lagman, MD, email communication, December 2023). Because of the severity of cluster headache, people generally require both acute and preventive treatment. We assumed that the number of people eligible for acute treatment would be the same as the number eligible for prevention.

Table 48: Volume of Intervention, Cluster Headache

Volume, n	Year 1	Year 2	Year 3	Year 4	Year 5
Ontario adult population (aged 18 to 90+ years)[a,b]	13,173,299	13,467,258	13,708,421	13,899,237	14,098,002
Population with cluster headache (0.1% prevalence)[c]	13,173	13,467	13,708	13,899	14,098
Population eligible for nVNS treatment (90% of the population with cluster headache)[b]	11,856	12,120	12,337	12,509	12,688
Population eligible for acute treatment (100%)	11,856	12,120	12,337	12,509	12,688
Population eligible for prevention (100%)	11,856	12,120	12,337	12,509	12,688

Abbreviations: nVNS, noninvasive vagus nerve stimulation.

[a] Ministry of Finance population projections, 2023.[110]

[b] M. Lagman, MD, email communication, May and December 2023.

[c] Schenck et al, 2020.[6]

Migraine

A Canadian study found that the prevalence of migraine in Ontario in 2010/11 was 8.8%.[7] An expert advised us that approximately 90% of people with migraine are eligible for nVNS treatment (i.e., nVNS is not contraindicated; M. Lagman, MD, email communication, December 2023). All people with migraine can use medication for acute treatment during an attack. However, about 25% of have migraine severe enough to receive preventive treatment.[19] We assumed that the number of people eligible for acute treatment would be much higher than the number eligible for prevention.

Table 49: Volume of Intervention, Migraine

Volume, n	Year 1	Year 2	Year 3	Year 4	Year 5
Ontario adult and adolescent population (aged 12 to 90+ years)[a]	14,180,195	14,482,945	14,727,596	14,921,727	15,124,605
Population with migraine (8.8% prevalence)[b]	1,247,857	1,274,499	1,296,028	1,313,112	1,330,965
Population eligible for nVNS treatment (90% of the population with migraine)[c]	1,123,071	1,147,049	1,166,425	1,181,800	1,197,869
Population eligible for acute treatment (100%)	1,123,071	1,147,049	1,166,425	1,181,800	1,197,869
Population eligible for prevention (25%)	280,768	286,762	291,606	295,450	299,467

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] Ministry of Finance population projections, 2023.[110]

[b] Ramage-Morin et al, 2014.[7]

[c] M. Lagman, MD, email communication, December 2023.

Current Intervention Mix

At present, nVNS is not publicly funded in Ontario. We assumed that all people in the current scenario received standard care, which included acute treatment and prevention.

Uptake of the New Intervention and New Intervention Mix

We assumed that nVNS would be used in addition to standard care. We also assumed that nVNS would be adopted relatively slowly, with uptake rates of 1% in year 1 to 5% in year 5 (Tables 50 to 53). For cluster headache, we assumed that the number of people eligible for nVNS for acute and preventive treatment would be the same (Table 48), so we also assumed that uptake for acute treatment and prevention would be the same.

Table 50: Uptake of nVNS and Standard Care in Ontario, Acute Treatment, Cluster Headache

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario					
Standard care, n	11,856	12,120	12,337	12,509	12,688
New scenario[a]					
Uptake rate for nVNS, %	1%	2%	3%	4%	5%
nVNS in addition to standard care, n	119	242	370	500	634
Standard care, n	11,737	11,878	11,967	12,009	12,054

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] The volume of interventions was calculated from the total number multiplied by the uptake rate of the new intervention. For example, in the new scenario, the total volume in year 1 is 11,856 and the uptake rate of nVNS is 1%, so the volume of nVNS in year 1 is 119 (11,856 × 1%).

Table 51: Uptake of nVNS and Standard Care in Ontario, Prevention, Cluster Headache

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario					
Standard care, n	11,856	12,120	12,337	12,509	12,688
New scenario[a]					
Uptake rate for nVNS, %	1%	2%	3%	4%	5%
nVNS in addition to standard care, n	119	242	370	500	634
Standard care, n	11,737	11,878	11,967	12,009	12,054

Abbreviations: nVNS; noninvasive vagus nerve stimulation

[a] The volume of interventions was calculated from the total number multiplied by the uptake rate of the new intervention. For example, in the new scenario, the total volume in year 1 is 11,856 and the uptake rate of nVNS is 1%, so the volume of nVNS in year 1 is 119 (11,856 × 1%).

Table 52: Uptake of nVNS and Standard Care in Ontario, Acute Treatment, Migraine

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario					
Standard care, n	1,123,071	1,147,049	1,166,426	1,181,801	1,197,869
New scenario[a]					
Uptake rate for nVNS, %	1%	2%	3%	4%	5%
nVNS in addition to standard care, n	11,231	22,941	34,993	47,272	59,893
Standard care, n	1,111,841	1,124,108	1,131,433	1,134,529	1,137,975

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] The volume of interventions was calculated from the total number multiplied by the uptake rate of the new intervention. For example, in the new scenario, the total volume in year 1 is 1,123,071 and the uptake rate of nVNS is 1%, so the volume of nVNS in year 1 is 11,231 (1,123,071 × 1%).

Table 53: Uptake of nVNS and Standard Care in Ontario, Prevention, Migraine

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario					
Standard care, n	280,768	286,762	291,606	295,450	299,467
New scenario[a]					
Uptake rate for nVNS, %	1%	2%	3%	4%	5%
nVNS in addition to standard care, n	2,808	5,735	8,748	11,818	14,973
Standard care, n	277,960	281,027	282,858	283,632	284,494

Abbreviation: nVNS noninvasive vagus nerve stimulation.

[a] The volume of interventions was calculated from the total number multiplied by the uptake rate of the new intervention. For example, in the new scenario, the total volume in year 1 is 280,768 and the uptake rate of nVNS is 1%, so the volume of nVNS in year 1 is 2,808 (280,768 × 1%).

Resources and Costs

We estimated annual costs per person from year 1 to year 5. All costs are in 2024 Canadian dollars. We used inputs for health care resource use and cost outputs from the primary economic evaluation, applying them over a 5-year period. We considered resource use associated with the health technology and the treatment of cluster headache or migraine, including costs incurred with the use of nVNS and medications. To estimate the budget impact of using nVNS for acute treatment, we considered only the cost of nVNS. To estimate the budget impact of using nVNS for prevention, we used the annual costs per person identified in the primary economic evaluation for each respective model.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses for both disease areas. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explore how the results are affected by varying input parameters and model assumptions.

Scenario Analyses

- Scenario 1 – the nVNS device is provided free for the first 93 days (i.e., at no cost to the Ministry of Health for 93 days). This scenario aimed to assess the budget impact when the first 3 months of treatment are covered by manufacturer.
- Scenario 2 – annual uptake rate increased to 2% per year, up to 10% uptake in year 5.
- Scenario 3 – annual uptake rate increased to 20% per year, up to 100% in year 5. This scenario assumed that uptake would reach 100% over 5 years.
- Scenario 4 – cost of the nVNS device, plus or minus 25% of the device cost (± $1,594 of the annual cost).

Results

Cluster Headache

Reference Case

Table 54 summarizes the budget impact of publicly funding nVNS for the acute treatment of cluster headache over the next 5 years. Publicly funding nVNS for acute treatment (i.e., device-only costs) in people with cluster headache would lead to additional costs of $0.76 million in year 1 up to $4.04 million in year 5, for a total of $11.88 million over 5 years.

Table 54: Budget Impact Analysis Results, nVNS for Acute Treatment, Cluster Headache[a]

Scenario	Budget impact, $ million[b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Budget impact[c]	0.76	1.54	2.36	3.19	4.04	11.88
nVNS costs	0.76	1.54	2.36	3.19	4.04	11.88
Acute medication costs	0.00	0.00	0.00	0.00	0.00	0.00
Preventive medication costs	0.00	0.00	0.00	0.00	0.00	0.00
Monitoring costs	0.00	0.00	0.00	0.00	0.00	0.00

Abbreviations: nVNS, noninvasive vagus nerve stimulation.

[a] nVNS costs were calculated based on the cost of the device and the number of people who would use it. Due to limited information, we did not estimate the impact of nVNS on medication and monitoring costs.

[b] In 2024 Canadian dollars.

[c] Results may appear inexact due to rounding.

Table 55 summarizes the budget impact of publicly funding nVNS for the prevention of cluster headache over the next 5 years. Publicly funding nVNS for the prevention of cluster headache would lead to additional costs of $0.63 million in year 1 (uptake: 1%) up to $3.37 million in year 5 (uptake: 5%), for a total of $9.92 million over 5 years (for a total of 1,865 people). Funding the nVNS device alone would cost $11.88 million over 5 years. Acute medication costs would be reduced in the new scenario, resulting in cost savings of $1.96 million over 5 years.

Table 55: Budget Impact Analysis Results, nVNS for Prevention, Cluster Headache

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Current scenario	29.83	30.50	31.04	31.47	31.924	154.765
Acute medication costs	20.40	20.83	21.23	21.52	21.83	105.83
Prevention medication costs	7.11	7.27	7.40	7.50	7.60	36.90
Monitoring costs	2.32	2.37	2.41	2.45	2.482	12.03
New scenario						
Standard care alone	29.53	29.89	30.11	30.21	30.27	150.07
Acute medication costs	20.19	20.46	20.59	20.66	20.74	102.62
Preventive medication costs	7.04	7.13	7.18	7.20	7.23	35.78
Monitoring costs	2.30	2.32	2.34	2.35	2.36	66.57
nVNS + standard care	0.93	1.90	2.90	3.92	4.97	14.62
nVNS costs	0.76	1.54	2.36	3.19	4.04	11.88
Acute medication costs	0.079	0.16	0.25	0.33	0.42	1.24
Preventive medication costs	0.071	0.15	0.22	0.30	0.38	1.12
Monitoring costs	0.023	0.047	0.072	0.098	0.12	0.37
Budget impact[b,c]	0.63	1.29	1.97	2.66	3.37	9.92
nVNS costs	0.76	1.54	2.36	3.19	4.04	11.88
Acute medication costs	−0.12	−0.26	−0.39	−0.53	−0.67	−1.96
Preventive medication costs	0.00	0.00	0.00	0.00	0.00	0.00
Monitoring costs	0.00	0.00	0.00	0.00	0.00	0.00

Abbreviation: nVNS; noninvasive vagus nerve stimulation.

[a] In 2024 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

Scenario Analysis

Table 56 summarizes the results of the 5 scenario analyses conducted for the acute treatment of cluster headache using nVNS. The scenarios yielded total 5-year budget impacts that ranged from $7.77 million to $237.69 million. Scenario 3, which involved increasing the annual uptake by 20% per year, up to 100% in year 5, had the greatest effect on the total budget impact.

Table 56: Scenario Analysis Results, nVNS for Acute Treatment, Cluster Headache

	Budget impact, $ million[a]					
Analysis	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b]**
Reference case	0.76	1.54	2.36	3.19	4.04	11.88
1: nVNS provided free for the first 93 days	0.49	1.01	1.54	2.08	2.64	7.77
2: Annual uptake of 2% per year, up to 10% in year 5	1.51	3.09	4.72	6.37	8.08	23.77
3: Annual uptake of 20% per year, up to 100% in year 5	15.1	30.88	47.15	63.74	80.81	237.69
4a: Cost of the nVNS device decreased by 25%	0.57	1.15	1.76	2.39	3.03	8.91
4b: Cost of the nVNS device increased by 25%	0.94	1.93	2.94	3.98	5.05	14.86

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] In 2024 Canadian dollars.

[b] Results may appear inexact due to rounding.

Table 57 summarizes the results of the 5 scenario analyses conducted for the prevention of cluster headache using nVNS. The scenarios yielded total 5-year budget impacts that ranged from $5.82 million to $198.43 million. Scenario 3, which involved increasing the annual uptake by 20% per year, up to 100% in year 5, had the greatest effect on the total budget impact.

Table 57: Scenario Analysis Results, nVNS for Prevention, Cluster Headache

	Budget impact, $ million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b]**
Reference case	0.63	1.29	1.97	2.66	3.37	9.92
1: nVNS provided free for the first 93 days	0.37	0.76	1.15	1.56	1.98	5.82
2: Annual uptake of 2% per year, up to 10% in year 5	1.26	2.58	3.94	5.32	6.75	19.84
3: Annual uptake of 20% per year, up to 100% in year 5	12.61	25.78	39.36	53.21	67.47	198.43
4a: Cost of the nVNS device decreased by 25%	0.44	0.91	1.38	1.87	2.37	6.97
4b: Cost of the nVNS device increased by 25%	0.82	1.68	2.56	3.46	4.38	12.89

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] In 2024 Canadian dollars.

[b] Results may appear inexact due to rounding.

Migraine

Reference Case

Table 58 summarizes the total budget impact of publicly funding nVNS use for the acute treatment of migraine over the next 5 years. Publicly funding nVNS (i.e., device-only costs) in people with migraine would lead to additional costs of $71.56 million in year 1 to $381.6 million in year 5, for a total of $1.12 billion over 5 years (for 176,330 people being treated with nVNS). There would be no change to the acute or preventive medication costs over 5 years.

Table 58: Budget Impact Analysis Results, nVNS for Acute Treatment, Migraine[a]

Scenario	Budget impact, $ million[b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Budget impact[c]	71.56	146.17	222.96	301.20	381.62	1,123.52
nVNS costs	71.56	146.17	222.96	301.20	381.62	1,123.52
Acute medication costs	0.00	0.00	0.00	0.00	0.00	0.00
Preventive medication costs	0.00	0.00	0.00	0.00	0.00	0.00
Monitoring costs	0.00	0.00	0.00	0.00	0.00	0.00

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] nVNS costs were calculated based on the cost of the device and the number of people who would use it. Due to limited information, we did not estimate the impact of nVNS on medication and monitoring costs.

[b] In 2024 Canadian dollars.

[c] Results may appear inexact due to rounding.

Table 59 summarizes the budget impact of publicly funding nVNS for the prevention of migraine over the next 5 years. Publicly funding nVNS for the prevention of migraine would lead to additional costs of $17.76 million in year 1 up to $94.69 million in year 5, for a total of $278.77 million over 5 years. Funding the nVNS device alone would cost $280.88 million over 5 years. Acute medication costs would be reduced in the new scenario, resulting in cost savings of $2.11 million over 5 years.

Table 59: Budget Impact Analysis Results, nVNS for Prevention, Migraine

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Current scenario	807.66	824.9	838.84	849.9	861.45	4,182.75
Acute medication costs	141.45	144.47	146.91	148.84	150.87	732.54
Prevention medication costs	614.47	627.59	638.19	646.61	655.4	3,182.27
Monitoring costs	51.74	52.84	53.74	54.44	55.18	267.95
New scenario						
Standard care alone	799.58	808.41	813.67	815.9	818.38	4,055.94
Acute medication costs	140.03	141.58	142.5	142.89	143.33	710.33
Preventive medication costs	608.33	615.04	619.05	620.74	622.63	3,085.79
Monitoring costs	51.22	51.79	52.12	52.27	52.43	259.82
nVNS + standard care	25.83	52.77	80.49	108.73	137.76	405.58
nVNS costs	17.89	36.54	55.74	75.3	95.41	280.88
Acute medication costs	1.28	2.61	3.99	5.39	6.83	20.1
Preventive medication costs	6.14	12.55	19.15	25.86	32.77	96.48
Monitoring costs	0.52	1.06	1.61	2.18	2.76	8.12
Budget impact[b,c]	17.76	36.27	55.32	74.74	94.69	278.77
nVNS costs	17.89	36.54	55.74	75.3	95.41	280.88
Acute medication costs	−0.13	−0.27	−0.42	−0.57	−0.72	−2.11
Preventive medication costs	0.00	0.00	0.00	0.00	0.00	0.00
Monitoring costs	0.00	0.00	0.00	0.00	0.00	0.00

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] In 2024 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

Scenario Analysis

Table 60 summarizes the results of the 5 scenario analyses conducted for the acute treatment of migraine using nVNS. The scenarios yielded total 5-year budget impacts that ranged from $734.80 million to $28.09 billion. Scenario 4b, which involved increasing the cost of the nVNS device by 25%, had the greatest effect on the total budget impact.

Table 60: Scenario Analysis Results, nVNS for Acute Treatment, Migraine

	Budget impact, $ million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b]**
Reference case	71.56	146.17	222.96	301.20	381.62	1,123.52
1: nVNS provided free for the first 93 days	11.55	23.59	35.98	48.61	61.59	734.80
2: Annual uptake of 2% per year, up to 10% in year 5	143.12	292.34	445.93	602.40	763.24	2,247.03
3: Annual uptake of 20% per year, up to 100% in year 5	1,431.17	2,923.45	4,459.25	6,024.04	7,632.43	22,470.34
4a: Cost of the nVNS device decreased by 25%	53.67	109.63	167.22	225.90	286.22	842.64
4b: Cost of the nVNS device increased by 25%	1,788.96	2,654.31	5,574.07	7,530.05	9,540.54	28,087.94

Abbreviation: nVNS, noninvasive vagus nerve stimulation.
[a] In 2024 Canadian dollars.
[b] Results may appear inexact due to rounding.

Table 61 summarizes the results of the 5 scenario analyses conducted for the prevention of migraine using nVNS. The scenarios yielded total 5-year budget impacts that ranged from $181.32 million to $6.98 billion. Scenario 3, which involved increasing the annual uptake rate by 20% per year, up to 100% in year 5, had the greatest effect on the total budget impact.

Table 61: Scenario Analysis Results, nVNS for Prevention, Migraine

	Budget impact, $ million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b]**
Reference case	17.76	36.27	55.32	74.74	94.70	278.77
1: nVNS provided free for the first 93 days	11.55	23.59	35.98	48.61	61.59	181.32
2: Annual uptake of 2% per year, up to 10% in year 5	35.51	72.54	110.64	149.47	189.38	557.54
3: Annual uptake of 20% per year, up to 100% in year 5	444.49	907.95	1,384.93	1,870.92	2,370.45	6,978.74
4a: Cost of the nVNS device decreased by 25%	13.28	27.12	41.37	55.89	70.82	208.49
4b: Cost of the nVNS device increased by 25%	22.22	45.40	69.25	93.55	118.52	348.94

Abbreviation: nVNS, noninvasive vagus nerve stimulation.
[a] In 2024 Canadian dollars.
[b] Results may appear inexact due to rounding.

Discussion

Cluster Headache

Our reference case results showed that, assuming a low uptake rate of 1% to 5% in years 1 to 5, publicly funding nVNS in addition to standard care for the prevention of cluster headache would lead to an additional cost of $9.92 million over the next 5 years. There were some potential cost savings associated with reduced acute medication use (i.e., $1.96 million over the next 5 years). For the acute treatment of cluster headache, we did not consider cost savings related to reduced medication use. Our analysis showed that the budget impact result was sensitive to assumptions related to uptake rates; the budget impact would increase substantially if uptake rates were higher.

Migraine

Our reference case results showed that publicly funding nVNS in addition to standard care for migraine would lead to a much larger budget impact than for cluster headache. This was because migraine is a highly prevalent condition, affecting about 8.8% of the population. In particular, publicly funding nVNS as an acute treatment for migraine would lead to a much larger budget impact compared to publicly funding it for prevention. This was because all people with migraine can use acute medication for a migraine attack, but only about 25% of people with migraine would experience symptoms severe enough to warrant preventive treatment.[19] The use of nVNS for prevention of migraine assumed a smaller volume of people with migraine and was therefore associated with lower total costs.

Equity Considerations

Our budget impact analysis did not include any particular equity considerations.

Strengths and Limitations

For the prevention of cluster headache and migraine, our estimates for the budget impact analysis were based on outputs from our primary economic analysis that were informed by effectiveness parameters from the clinical evidence review, and by cost parameters derived largely from Canadian sources.[91] We validated our assumptions and estimates with clinical experts who have expertise in the use of nVNS for cluster headache and migraine. Our analysis provided detailed results categorized by type of use (i.e., for acute treatment or prevention) for cluster headache or migraine.

Our budget impact analysis was subject to certain limitations. First, it was based on the economic model developed for our primary economic evaluation, so it is limited by the data that informed the evaluation. Second, uptake rates for nVNS over the next 5 years may be highly uncertain, and we assumed that rates would be the same for people with cluster headache and people with migraine. We performed scenario analyses that varied uptake rates to address these uncertainties. Third, our budget impact estimates of nVNS use are based on a single nVNS device (i.e., gammaCore). If other nVNS devices (with different costs) become available in Ontario, the applicability of our analysis may be limited. Last, although cluster headaches and migraine are medically distinct conditions, the 2 conditions share some similarities and people with cluster headache may be misclassified as having migraine or a different type of headache. Such potential misclassification could influence budgetary considerations, especially if the nVNS device receives public funding for different conditions. To address this, precise

diagnostic criteria to differentiate between cluster headache and migraine are crucial, particularly in relation to eligibility for publicly funded nVNS treatment.

Conclusions

- Publicly funding nVNS for the acute treatment of cluster headache would lead to additional costs of $0.76 million in year 1 to $4.04 million in year 5, for a total of $11.88 million over 5 years.
- Publicly funding nVNS for the prevention of cluster headache would lead to additional costs of $0.63 million in year 1 to $3.37 million in year 5, for a total of $9.92 million over 5 years.
- Publicly funding nVNS for the acute treatment of migraine would lead to additional costs of $71.56 million in year 1 to $381.62 million in year 5, for a total of $1.12 billion over 5 years.
- Publicly funding nVNS for the prevention of migraine would lead to additional costs of $17.76 million in year 1 to $94.69 million in year 5, for a total of $278.77 million over 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of cluster headache and migraine, as well as the preferences and perceptions of patients, family, and care partners in relation to noninvasive vagus nerve stimulation (nVNS).

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other care partners, and the person's personal environment. Engagement also provides insight into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[111-113] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider as a way of understanding the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with cluster headache and migraine via direct engagement.

Direct Patient Engagement

Methods

Partnership Plan

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with cluster headache and migraine, and those of their families and other care partners. We engaged people via telephone interviews; we also conducted an online survey to extend participation opportunity to those who contacted us after interviews were closed.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with cluster headache and migraine, as well as those of their families and care partners.[114] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of methodology.

For our interview and survey questions, we leveraged Migraine Canada's 2021 quality-of-life survey.[115] The survey aimed to better understand the burden of living with migraine, its impact on quality of life, and the needs of Canadians living with migraine. The survey found that migraine negatively affected people's quality of life, mental health, ability to work, social life, and relationships. The survey report recommended improved access to treatment by expanding coverage for devices and injections.

Participant Outreach

We used an approach called purposive sampling,[116-119] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached advocacy groups such as Migraine Canada to spread the word about this engagement activity and to contact people with cluster headache or migraine, including those with experience of nVNS.

Inclusion Criteria

We sought to speak with adults who had lived experience of cluster headache or migraine, in particular those who had experience with nVNS. However, people did not need to have direct experience with nVNS to participate.

Exclusion Criteria

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

Participants

For this project, we spoke with 18 participants in total: 3 with cluster headache, and 15 with migraine. Only 1 participant had experience with nVNS. The survey had 6 participants, all with migraine (1 had both cluster headache and migraine).

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 8). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 30 to 60 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[120] Questions focused on the impact of cluster headache and migraine on people's quality of life, the journey to diagnosis, treatment options explored, and preference and decision-making factors related to nVNS. See Appendix 9 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts and survey results. The grounded-theory approach allowed us to organize and compare information on

experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[121,122] We used the qualitative data analysis software program NVivo[123] to identify and interpret patterns in the data. The patterns we identified allowed us to describe the impact of cluster headache and migraine on people's life and decision-making factors related to nVNS.

Results

Living With Cluster Headache and Migraine

Cluster Headache

People with cluster headache commented on the intensity of the pain that they experienced during a headache episode.

> *It is an intense pain, always on the left side. The eye starts watering and the pain lasts typically, for me, 15 minutes to half an hour.*
>
> *The cluster headaches were mostly like a ring of pain around my head, behind my eyeballs, and the severity, I would say, was moderate to high.*
>
> *Headache starts within a couple of minutes and goes from a shadow headache to being extremely painful within about 3 to 4 minutes … I can be in severe pain, rocking backwards and forwards, and unable to tolerate any light.*

Migraine

People with migraine described different symptoms, including brain fog, confusion, sensitivity to light and sound, blurred vision, aura, dizziness, numbness of the body, and headache. These symptoms were persistent and lasted for multiple days, having a negative impact on their quality of life.

> *I experience brain fog, confusion, to the point where some days it's very difficult to speak and process information.*
>
> *Inability to function with light or sound at all around me, dizziness, and falling down.*
>
> *I started out having visual symptoms, like blurred vision in 1 of my eyes along with the bad headache.*
>
> *My symptoms always started with an aura. And with the aura I would get numbness on half of my body, usually my left side.*
>
> *Every time I have a migraine, each of these episodes will last from 3 to 5 days where I'm completely debilitated, just puking and can't get out of bed, usually with temporary paralysis on 1 side of my body.*

People mentioned that weather conditions, food, or smells would usually trigger their migraine.

> *It [migraine] used to be triggered mainly by changes in barometric pressure, mainly when any kind of form of precipitation moved in: fog, snow, rain, sleet,*

hail, any kind of precipitation, I would get a migraine. Sometimes they last for 12 hours, sometimes they last for 3 days.

Cigar smoke would trigger me; possibly chocolate and perfume as well. Anything just sent me over the edge.

People also reported excruciating pain during their migraine episode, which caused them emotional distress.

The pain is very sudden. It comes on very suddenly and very strong … It's like an explosive pain that comes, and I can't do anything once it hits.

Sometimes I lie in my bed and cry because the pain is so bad.

When I have a migraine, I am debilitated in all aspects. I have pain so intense that I am unable to sleep.

I closeted myself in the women's bathroom in the dark, crying, pushing my head against the wall, because that is something that helps relieve the pain.

I usually have very sharp and achy pains in my neck and shoulders. And then it's in my head as well. It's usually 1-sided. Usually a stabbing, throbbing kind of pain.

Impact on Day-to-Day Life

Cluster Headache

People with cluster headache mentioned that headaches affected their concentration while they were driving. They talked about impact of headaches on their day-to-day life, including lack of sleep.

I would be getting headaches when I was driving. That was terrifying, and I'd have to pull over.

When I first developed them [cluster headaches], I was travelling a lot, so I would sleep in hotels, and when I got the headaches I would not be getting any sleep.

Migraine

People with migraine described its effect on their day-to-day life, including difficulty leaving the bed to perform household chores and inability to concentrate while driving.

[When migraines hit] you're in bed for the day. You can't do any cooking or housework.

I am virtually incapacitated by my migraines. Bright lights, most sounds, and pretty well any movement is uncomfortable. As you can imagine, there is not much I can do in that condition. Not too long ago, I had a migraine while I was driving and it became so severe I had go park and get someone to come pick me up and take me to hospital.

It definitely interfered with concentration, with just even the ability to safely operate cars.

People also expressed their frustration with their reduced quality of life as a result of their migraines and not knowing how their day would be affected by their symptoms.

> *Overall quality of life has been impacted immensely. I feel like a stranger in my own mind and body. Migraine has robbed me of an identity beyond survival and management of the disease. I never know what kind of day I am going to wake up to, or what will transpire throughout the day. [I am] never fully trusting [that] a mild day will not turn into a red, full-blown attack.*
>
> *I am grieving not only my ability to mask and manage the pain and symptoms as I previously was, but also the years and quality of life lost from tolerating more than I should have. It quite literally impacts every single aspect of life.*

Impact on Work

Cluster Headache

People with cluster headache experienced decreased productivity at work due to loss of focus and concentration caused by a headache.

> *It [cluster headache] absolutely affected my work; I had a very cognitively high-functioning job, and it was extremely difficult to concentrate.*
>
> *It [cluster headache] has an impact on my job, on my performance, on my ability to concentrate and function.*
>
> *It is excruciatingly painful and very difficult to continue my work generally while I'm going through the headaches. They do tend to come on at the same time of day, which is approximately 10 in the morning.*

Migraine

People explained that migraine contributed to decreased focus, leading to decreased productivity and performance at work, as well as repercussions for their career path. Most had to take multiple days off work or quit their jobs because their symptoms were persistent and prevented them from working.

> *I'll take a sick day at work. Or if it develops midday while I'm at work, I'll continue working but my productivity decreases, I work slower, and I can't focus as much.*
>
> *I missed a lot of work because of migraines.*
>
> *I was only able to work for about 3 months, and then I was let go due to my migraines and having to miss time. Now I'm still unable to work.*
>
> *I had to leave my career that I worked so hard for, and I had to take a step back to do more casual work on a part-time basis that could be more flexible, so that I stopped missing work.*

People also experienced distrust from their employers when they missed multiple days at work due to their migraine. Furthermore, it was a challenge for them to be hired because they were considered unreliable due to their condition.

I was missing extraordinary amounts of work due to my migraines, and [employers] didn't believe me.

On days when I did take time off, I experienced a lot of disbelief [from employers] about the extent of my symptoms.

I'm lucky if I get any work at all because who's going to hire someone that can't 100% promise to show up to every shift.

Impact on Social Life and Family Relationships

Cluster Headache

People with cluster headache mentioned having to cancel social plans due to their headache. They avoided social gatherings that could accidentally trigger a headache.

In the old days I tended to shy away from socializing … because if someone gives me a drink and I don't realize there's alcohol in it, then that could easily set me off [trigger a headache].

I've had to cancel a lot of events or leave early from the event.

It kind of affected my daily life with family time because I couldn't concentrate.

Migraine

People's social life and family relationships were negatively affected by their migraine. Participants explained that they found it difficult to commit to plans because of the unknown timing of their migraine onset. This limited their social interactions and made it difficult to engage with others and form relationships. Some participants also spoke about avoiding places of social gathering with bright lights and loud noise that could trigger their symptoms.

Socially, it's very hard to commit to any plans because you don't know when you're going to have an attack.

It affects my ability to socialize with friends or family. We have to cancel on a lot of things due to my migraines. Everything is very dependent on my migraines.

I had to stop going to indoor events with flashing lights and/or loud music or loud sounds unless I was able to preplan a quick exit if needed. [I felt] embarrassment about the times when I didn't catch the onset of a complex hemiplegic migraine quickly enough, resulting in what looks like a stroke. An ambulance is called unless I am with a friend who knows what is happening and is able to speak for me.

People reported feeling excluded from social gatherings due to their uncertain availability.

It got to the point where my social circle just wouldn't ask me to go out anymore because they were sick and tired of me cancelling at the last minute.

People stop inviting you to things when you often can't make it or have to leave due to migraine.

Impact on Mental Health

Cluster Headache

People with cluster headache reported experiencing trauma as a result of repetitive, severe headache. They also mentioned the impact on their mood and fatigue during their headache episode. One person had suicidal thoughts due to the intensity of the pain.

> *They call them "suicide headaches," and there were often times where I couldn't stand it anymore, but I persevered.*
>
> *Just because it's such a violent headache that it is repeating, it is traumatizing me each time.*
>
> *I can be become quite moody, tired, and just grumpy.*

Migraine

People's mental health was negatively impacted by migraine. They reported having depression, anxiety, and suicidal ideation associated with their migraine. Their anxiety stemmed from not knowing when a migraine would start and how long it would last for. They described feeling hopeless and frustrated because of the absence of cure for their condition and the general lack of understanding related to a chronic illness such as migraine.

> *I've been diagnosed with reactive depression to chronic illness. I've been suicidal over this. It's a massive struggle.*
>
> *There's been times where it's greatly affected my mental health to the point of not wanting to live … It makes you very depressed, and certainly there's some anxiety there, too, because you never know when a migraine will start and how long it will stick around for.*
>
> *It feels really frustrating and kind of hopeless because there's no cure for this.*
>
> *It's extremely depressing and frustrating because people don't really understand chronic pain … dealing with a chronic illness and being in pain can be very depressing.*

Some people mentioned attending therapy and taking medication to cope with their mental health struggles.

> *I'm in therapy right now just to watch for my emotional regulation, stress factors, and things like that.*
>
> *I do see a therapist to help me cope with dealing with a chronic illness.*
>
> *I do take antidepressants and antianxiety medication.*

Impact on Care Partners

People reported that their relationship with their care partners was strained due to their condition. They explained that their care partners experienced emotional distress, worry, and lack of companionship as

a result of their migraine. When experiencing migraine, people were unable to work and attend to household duties, so the responsibility fell on care partners.

> *My partner has to jump in and help a lot, and that affects his mental health … On any given day after work, he comes home and he's tired. And the first thing he sees is that I'm sick and I'm lying in bed, and everything's a mess.*
>
> *Growing up, it's certainly impacted my parents, and their concern for me, and how it's going to affect my life. And they were, I think, always pretty worried about me. And now, with my husband, he definitely is always checking in and wondering.*
>
> *Lack of companionship. I'm just not here for him [my partner].*
>
> *It does put some strain on my relationship with my partner when I'm having a lot of migraines.*

People also described how they relied on their care partners due to their migraine symptoms.

> *It's very difficult for my partner because I'm dependent on him both financially and like everything in my life.*
>
> *My husband does everything in the house.*

Treatment: Medication

Cluster Headache

People with cluster headache mentioned trying medications for acute treatment and preventive medications, such as verapamil and oxygen inhalation therapy. Some said that they experienced pain relief from with medications, but others also expressed disappointment over about the lack of effective treatment options for cluster headache.

> *Four years ago I started getting oxygen delivered, and that definitely helped when I felt a headache coming on. If I get the high-flow oxygen for 15 minutes, I usually knock them down pretty good.*
>
> *I was on verapamil; that really didn't do anything.*
>
> *I've tried nasal spray quite recently, and some nerve block injections into the head.*
>
> *There weren't very many treatment options available to cluster headache patients.*

Migraine

People with migraine spoke about the different acute and preventive medications they use to manage their symptoms. The effectiveness of these medications varied from person to person; some experienced pain relief and others did not see a positive effect. Most reported that taking medication for prevention lessened the frequency and intensity of their pain, but it did not fully prevent a migraine.

I take extra-strength Tylenol to manage pain and Gravol to manage nausea.

I've tried at least 20 different preventive medications, from beta blockers, calcium channel blockers, sedatives, benzodiazepines and off-label usage … None of it worked for me.

Now because my headaches got more frequent, my doctor started me on a beta blocker. I'm taking a medication called propranolol. I take that twice a day and I've been on it for about a year, and it has worked really well to prevent migraines.

I usually take Advil 400 mg, and if I take it soon enough sometimes I can lessen the migraine, but it never goes away.

I have tried all preventives imaginable, but only nonprescription supplements have had any noticeable effect on frequency and intensity.

People mentioned taking acute medications such as triptans for their migraine. They also expressed concerns about taking drugs with addictive effects, such as narcotics.

We went through each new triptan in the market, and so far we have found 1 that works as an abortive [i.e., acute treatment].

I also depend on a heavy opiate nasal spray to get me through a migraine.

I have prescriptions for narcotics and triptans, but I don't tend to take them because they lose their effectiveness and opioids are very hard on your system and notoriously addictive.

Adverse Effects

People with cluster headache and migraine described the adverse effects that they experienced with medications, ranging from drowsiness, nausea, and brain fog to dangerously low blood pressure, suicidal ideation, and heart issues that required hospitalization.

I did have like a lot of fatigue with it [medication]. I just felt worn down and drowsy.

It [medication] makes your brain foggy, you get nauseous, or [you have] issues with going to the bathroom.

I tried a number of medications, some of which I had to stop because the side effects were so severe they caused suicidal ideation.

My blood pressure dropped to dangerous levels. It would have me passing out.

The effect it [medication] had on me was that it gave me a mini heart attack. The day that I had to take it, I also had to be taken away by ambulance to the hospital.

I had arteritis that required weeks of hospitalization and testing, and it turned out to be a side effect of the drug that I was taking for migraine.

I was treated with corticosteroids – very effective for cluster headaches, but also at high doses it's very disruptive to sleep.

Treatment: Alternative Options

People with cluster headache and migraine also reported trying alternative treatment options such as relaxation and massage, supplements, cognitive behavioural therapy (CBT), hormone therapy, chiropractic, acupuncture, and Botox injections.

> *Outside of medications, I did CBT, mindfulness activities, getting massages, and acupuncture.*
>
> *What tends to happen with the cluster headache is the body gets tight and contorted, so the massages do help.*
>
> *I've tried different supplements like magnesium, riboflavin, coenzyme Q10.*
>
> *I'm doing hormonal therapy because my migraines are definitely hormone-related. I have also done acupuncture and massage therapy.*
>
> *I tried Botox, which helps to an extent, but it wasn't very practical.*

People also incorporated lifestyle modifications to manage their symptoms and avoid triggers.

> *Lifestyle changes like removing coffee and alcohol … and at the time I was smoking, but when I got cluster headaches, I discontinued smoking.*
>
> *I do a lot of like lifestyle stuff. I avoid all my trigger foods and anything that's inflammatory. I also avoid high-physical-stress activities that tend to also trigger migraines.*

Some people mentioned using noninvasive neuromodulation devices to treat their migraines, with effectiveness varying from person to person.

> *I've used [a noninvasive trigeminal nerve stimulation device] both acutely and preventatively for a couple of months, and I found that it makes my whole body tense up and my headaches worse.*
>
> *I use a noninvasive trigeminal nerve stimulation device regularly with some success on milder migraines.*

Treatment: nVNS

Lack of Awareness of nVNS

Most people were not familiar with nVNS as a treatment option for cluster headache and migraine. Those who were familiar with it found out about nVNS through clinical trials for other conditions such as depression.

> *I've never heard of it. I looked it up after getting your correspondence.*
>
> *I'm not aware of them.*
>
> *I learned about them about a year ago … I saw some study about them.*
>
> *I only heard about it fairly recently, and that was that was in terms of depression, not in terms of migraines.*

However, people were open to trying nVNS for their cluster headache and migraine because most of them were not getting relief from their medication and they appreciated the noninvasiveness of this treatment option.

> *I'd be willing to try anything if it's going to help with this and improve my quality of life.*
>
> *I haven't personally tried one yet, but I'm definitely interested in trying it.*
>
> *I would definitely try it out because medication does not help.*
>
> *I would absolutely try this device because it's not an invasive technique.*

Decision-Making Factors

Cost

Most people with cluster headache and migraine said that cost would be the primary deciding factor for them in choosing whether or not to try nVNS. They said that the high out-of-pocket cost for the device, including ongoing maintenance costs, would be a barrier.

> *I guess cost would be the number-one deciding factor.*
>
> *It would be a significant barrier, and I would never pay $6,000 a year to try that. That's just crazy-expensive.*
>
> *I think the nerve stimulation thing that I was looking at, it's not a 1-time fee. It's something where you have to subscribe to it or continue to pay for it. And that felt really steep.*
>
> *These [nVNS] devices are not cheap. They're very expensive. Plus, you have to get some renewal things with it. So I think a lot of people who could benefit from them will be unable to because they can't afford it.*
>
> *I have good benefits, but it doesn't mean I have a lot of extra money. So I would say that having this compensated or paid for by the government would be a deciding factor.*

Given the high out-of-pocket cost for nVNS, people said that they would be willing to try it if it were covered by the government or their insurance.

> *If it was covered by the government, I would 100% be trying it.*
>
> *I would need to look into whether this could be expensed through my medical benefits.*

Safety and Effectiveness

People with cluster headache and migraine also said that safety and effectiveness were important decision-making factors. Safety was mostly associated with a lack of side effects; effectiveness was associated with the relief of symptoms. Ease of use was important as well.

> *I know it's supposed to alleviate pain, but I guess I would be concerned that I would have additional side effects while having it.*

If it's been proven to work in alleviating symptoms, then I would be more inclined.

Decision-making factors for me would be lack of side effects, ease of use, and whether or not it interferes with things that I need to do day to day.

[The decision-making factors are …] the portability of [the nVNS device], how you use it, and how it would fit into my lifestyle.

Preference for a Noninvasive Option

People noted the importance of noninvasive treatment options for cluster headache and migraine. They said that they would be willing to try nVNS because it is noninvasive. They also expressed concerns about the side effects they experience from medications and other invasive treatment options, making nVNS an ideal treatment option.

Because it's noninvasive and I've had a lot of brain surgeries, and I really can't put myself through that again. I know there's a similar device that's implanted into people's heads to stimulate the vagus nerve – I wouldn't consider that. But this [nVNS], I would absolutely jump at the chance.

I don't like taking medications, so that [nVNS] would be great.

I think that [the fact that it is noninvasive] is a deciding factor for sure. It's not cutting or exploring deep into the brain, so it's noninvasive. I think that's a big plus. I would say that it also doesn't have side effects like medications.

I'm on various heavy-duty drugs, but I would rather suffer through the pain than have another side effect to deal with. Which is why these noninvasive vagus nerve stimulators may be more worthwhile: because there are really no side effects.

Experience With nVNS

Only 1 person with migraine had experience with nVNS as part of a clinical trial. They described their overall experience with an nVNS device that was worn around the neck for 30 minutes per day for 3 months. They explained that the device was easy to use and was paired to an application on their cell phone to stimulate the vagus nerve. They reported that they didn't experience any positive effects for their symptoms while using the device, but they were still willing to try another type of nVNS device.

It [nVNS device] would be worn around your neck to stimulate the vagus nerve and to hopefully reduce pain … I signed up to be a member of that trial.

The device is paired with an app on my phone, and I just held it around my neck tightly with an elastic band like they showed us in the in the study material, and all we had to do was log into the app and run that specific program to stimulate the vagus nerve.

It was 30 minutes a day, every day, for 3 months.

I used it every day like I was supposed to, and I felt no effect from it, but that wouldn't keep me from trying something else [i.e., a different nVNS device]

Barriers to Treatment

People spoke about the barriers they faced while trying to access treatment for cluster headache and migraine. They described a lack of access to specialized care, challenges in getting a proper diagnosis, out-of-pocket cost for treatment, and stigma related to cluster headache and migraine.

Lack of Access to Specialist Care

People with cluster headache and migraine pointed to a lack of access to specialist care, including headache specialists and neurologists. In particular, those who lived in Northern Ontario mentioned that they were unable to see specialists in their community. Often, they would have to travel a long distance to seek care. People also noted the challenge of being on a long waiting list to see a neurologist.

> *People wait for years and years on a list to get a headache specialist. They're often at least 10 years into their migraine journey, if not much further along, before they ever get a migraine specialist.*
>
> *There is no like regular neurologist here in my small community, so I have never seen a neurologist. My doctor has never referred me to one.*
>
> *I'm in Northern Ontario, so there are no neurologists around here.*
>
> *I live in an underserviced area for medical professionals, to go see a neurologist. I had to somehow drag myself, with chronic migraines, to 2½ hours away.*
>
> *If I need to change my medications to something else, it takes almost a year to see a neurologist here. You're on a waiting list, especially if it's not urgent.*
>
> *I had to wait a year to get an appointment with a neurologist. That's a barrier.*

One person expressed frustration that they were unable to be treated by a neurologist for their migraine because they had been taking narcotics for another chronic pain condition.

> *It all comes down to being someone who is on narcotic pain meds prescribed by neurologists for a chronic pain condition, and now they won't take me [to treat migraine] because I'm on narcotic pain meds, so I'm tapering off the pain meds to get a neurologist to treat me [for migraine].*

Challenges in Getting a Proper Diagnosis

People with cluster headache and migraine described the challenges they faced in getting a proper diagnosis. Some were misdiagnosed, which exacerbated their condition; others had to wait a long time before they were officially diagnosed. People also explained that their clinicians would dismiss their symptoms as a normal headache, which further delayed their diagnosis and treatment.

> *I went through that kind of misdiagnosis, and my migraines got much worse, because the nasal sprays [prescribed for the misdiagnosed condition] were triggering my migraine.*
>
> *I had a lot of difficulty getting a diagnosis. I knew what it was, but every time I went to see a doctor they were like, "Yeah, people get headaches."*

I had a family doctor, but she didn't have a lot of experience with migraine. And I feel like she really just thought it was a regular headache.

It was quite long, that it took me 10 years to get properly diagnosed with cluster headaches.

Back then, people just assumed that [cluster headaches] were either a form of migraine or that they were just standard headaches.

Out-of-Pocket Costs for Treatment

People with migraine reported the financial burdens they faced when paying out of pocket for their treatments, including medications and alternative treatments. Additional costs such as transportation to doctor's appointments were also noted as a barrier.

The cost of pharmaceuticals to treat migraines and my associated disease, cyclic vomiting syndrome, are astronomical, even with my insurance.

The [biggest] financial burden has been exploring alternatives to prescription medicine.

I've spent thousands of dollars on medications over the years, and that's even with health insurance.

I do not have a drug plan, so all costs dealing with migraine come out of my pocket.

They suggested Botox injections, but it would have been $500 at the time, and I'm on disability benefit. I don't have $500, and that's on top of the costs of getting to hospital appointments, including the cost of gas and parking.

People with cluster headache also mentioned the high out-of-pocket cost for oxygen therapy and the financial burden of medications for cluster headache and other chronic conditions.

I went through huge tanks [of oxygen], sometimes 1 of those a week, so the only challenge I had was the cost, as it was not covered by my insurance.

It's very expensive, there is out-of-pocket expenses already with cluster headaches to do with oxygen, and other medications for other conditions like HIV, which I have.

Stigma Related to Cluster Headache and Migraine

People with migraine and cluster headache experienced stigma related to their condition from family members, employers, and clinicians. They experienced emotional distress because people did not believe the intensity of their pain or had misconceptions that children or young adults do not get migraine.

I had 1 brother-in-law that accused me of making this whole thing up and gaslighting. That was very hurtful. But that's how people perceive these things.

I would go in and talk to [employers] about this, about how sick I am. And they're like, well, you're young, you don't look sick … And she didn't really believe me.

It's also depressing when you go to the hospital and doctors think you're just seeking drugs … Nurses say you're just drug-seeking or they minimize the pain.

The thinking at the time was that children didn't have headaches, and that it was psychosomatic. I had neurologists telling me that the headaches would go away when I got married and had children.

People who don't get migraines think that it's just a headache. So, take your Tylenol and you're done. But for people who suffer from migraines, it's very debilitating.

Discussion

All participants had lived experience with cluster headache or migraine. They reported the negative impacts of cluster headache or migraine on their day-to-day activities, work, social life and family relationships, and mental health. They spoke about managing their condition and the different treatment options they had tried. One participant spoke about their experience with nVNS. All participants were open to trying nVNS for cluster headache or migraine. Participants described the importance of expanding access to noninvasive treatment options such as nVNS.

Our analysis was limited by a lack of geographic representation among participants, most of whom lived in southern Ontario. However, we did have 2 participants from Northern Ontario. We also had low representation from people who had direct experience with nVNS treatment; this can be attributed to the limited availability in Ontario of nVNS treatment for cluster headache and migraine.

Conclusions

The people we spoke with described the negative impact of living with cluster headache and migraine. They reflected on their experiences of seeking effective treatment for their condition. Most participants who took medications commented on the positive impact of their medications on relieving their symptoms; however, some reported adverse effects from their medications. One participant who had tried nVNS did not see positive effects on their symptoms, but all participants were interested in trying nVNS, highlighting the importance of noninvasive treatment options for cluster headache and migraine.

Conclusions of the Health Technology Assessment

Results from this clinical review of the effectiveness and safety of nVNS suggest that people with cluster headache or migraine may achieve clinical benefits from using the device, with little to no impact in terms of serious adverse events or device-related adverse events. However, the extent of any potential benefit is unclear, and results were generally of very low to moderate quality, depending on the specific headache disorder and the indication for its use.

For the prevention of cluster headache, nVNS in addition to standard care (compared with standard care alone) was associated with an additional 0.1945 QALYs and an additional cost of $5,317 per person, resulting in an ICER of $27,338 per QALY gained over 1 year. For the prevention of migraine, nVNS in addition to standard care (compared with standard care alone) was associated with minimal change in QALYs and an additional cost of $6,324, resulting in an ICER of $952,116 per QALY gained over 1 year. The findings of our Ontario-based cost-effectiveness analyses for the preventive treatment of cluster headache and migraine should be interpreted with caution because of the low quality of the clinical inputs used to inform the economic modelling. The cost-effectiveness of nVNS for the acute treatment of both conditions for Ontario is unknown.

Our budget impact analyses for Ontario found that publicly funding nVNS for the acute and preventive treatment of cluster headache would lead to additional $11.88 million and $9.92 million over 5 years, respectively. Publicly funding nVNS for the acute and preventive treatment of migraine would lead to additional $1.12 billion and $278.77 million over 5 years, respectively.

The people we spoke with described the negative impact of living with cluster headache and migraine. They reflected on their experiences of seeking effective treatment for their condition. One participant who had tried nVNS did not see positive effects on their symptoms, but all participants were interested in trying nVNS, highlighting the importance of noninvasive treatment options for cluster headache and migraine.

Abbreviations

CGRP: calcitonin gene-related peptide

CI: confidence interval

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICER: incremental cost-effectiveness ratio

NICE: National Institute for Health and Care Excellence

NSAID: nonsteroidal anti-inflammatory drug

nVNS: noninvasive vagus nerve stimulation

QALY: quality-adjusted life-year

PRISMA: Preferred Reporting for Systematic Reviews and Meta-Analyses

RCT: randomized, controlled trial

WTP: willingness to pay

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cohort model: In economic evaluations, a cohort model is used to simulate what happens to a homogeneous cohort (group) of patients after receiving a specific health care intervention. The proportion of the cohort who experiences certain health outcomes or events is estimated, along with the relevant costs and benefits. In contrast, a microsimulation model follows the course of individual patients.

Cost–consequence analysis: A cost–consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of two or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness analysis: Used broadly, “cost-effectiveness analysis” may refer to an economic evaluation used to compare the benefits of 2 or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, “cost-effectiveness analysis” may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost-minimization analysis: In economic evaluations, a cost-minimization analysis compares the costs of two or more health care interventions. It is used when the intervention of interest and its relevant alternative(s) are determined to be equally effective.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of 2 or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of 2 or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of 5 questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are 3 response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes 5 response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[124] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all people and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Generic preference-based measures: Generic preference-based measures are generic (i.e., not disease specific) instruments used to obtain the quality-adjusted weight (i.e., the utility value) of being in a given health state. Generic preference-based measures typically consist of a self-completed questionnaire, a health-state classification system, and a scoring formula that calculates the utility value. Examples include the Health Utilities Index Mark 3 (HUI3), the EQ-5D, and the Short Form–Six Dimensions (SF-6D). The quality-adjusted weights are obtained from the public or from patients, who are provided with a descriptive profile of each predefined health state and asked to fill out a questionnaire. The benefit of using a generic instrument is the ability to obtain utility values that are comparable across different health care interventions and diseases.

Health inequity: Health inequities are avoidable inequalities in health between groups of people within countries and between countries.[125] These inequities arise from inequalities within and between societies. Social and economic conditions and their effects on people's lives determine their risk of illness and the actions taken to prevent them becoming ill or treat illness when it occurs.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Horizontal equity: Horizontal equity requires that people with like characteristics (of ethical relevance) be treated the same.

Human capital approach: In economic evaluations, the human capital approach is used to estimate a monetary value that represents a person's loss of productivity due to disability, illness, or premature death.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Markov model: A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Monte Carlo simulation: Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic analysis.

Multiway sensitivity analysis: A multiway sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying a combination of model input (i.e., parameter) values simultaneously between plausible extremes to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Natural history of a disease: The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying 1 model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by 1 quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Risk difference: Risk difference is the difference in the risk of an outcome occurring between 1 health care intervention and an alternative intervention.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Short-Form–Six Dimensions (SF-6D): The SF-6D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The classification system consists of 6 attributes (physical functioning, role limitations, social functioning, pain, mental health, and vitality), each associated with 4 to 6 levels, thus producing a total of 18,000 possible unique health states. A scoring table is used to convert SF-6D scores to health state values.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where 2 technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Vertical equity: Vertical equity allows for people with different characteristics (of ethical relevance) to be treated differently.

Visual analogue scale (VAS): The visual analogue scale (VAS) is a direct method of measuring people's preferences for various health states. Respondents are first asked to rank a series of health states from least to most preferable. Then, they are asked to place the health states on a scale with intervals reflecting the differences in preference among the given health states. The scale ranges from 0 (worst imaginable health) to 100 (best imaginable health). The value of a respondent's preference for each health state is given by their placement of each health state on the scale.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search Date: September 13, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 6, 2023>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 36>, Ovid MEDLINE(R) ALL <1946 to September 12, 2023>
Search Strategy:

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1 exp Migraine Disorders/ (112454)
2 (migrain* or (sick adj headache*)).ti,ab,kf. (118769)
3 Cluster Headache/ (8912)
4 ((cluster* adj5 headache*) or (histamin* adj3 cephalgi*) or (neuralgia* adj3 ciliar*) or horton* syndrome*).ti,ab,kf. (10018)
5 or/1-4 (148465)
6 Transcutaneous Electric Nerve Stimulation/ (10813)
7 Vagus Nerve Stimulation/ and (noninvasiv* or non invasiv* or less invasiv* or portab* or transcutaneous*).ti,ab,kf. (2453)
8 (((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous* or cervical*) adj5 (vagal nerve* or vagus nerve*) adj5 stimulat*) or nVNS).ti,ab,kf. (3279)
9 ((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous*) adj3 (neurostimulat* or neuromodulat*)).ti,ab,kf. (3520)
10 (gammacore* or gamma core* or sapphire* or electrocore* or RSK medical* or cerbomed*).ti,ab,kf. (7089)
11 or/6-10 (24134)
12 5 and 11 (1021)
13 exp Animals/ not Humans/ (16348105)
14 12 not 13 (847)
15 limit 14 to english language [Limit not valid in CDSR; records were retained] (809)
16 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6516503)
17 15 not 16 (784)
18 17 use medall,coch,cleed (256)
19 ((Letter not (Letter and Randomized Controlled Trial)) or Conference proceeding or Editorial or Comment or Trial registry record).pt. (4932715)
20 15 not 19 (706)
21 20 use cctr (64)

22 18 or 21 (320)
23 exp migraine/ (112454)
24 (migrain* or (sick adj headache*)).tw,kw,kf. (119267)
25 exp cluster headache/ (9709)
26 ((cluster* adj5 headache*) or (histamin* adj3 cephalgi*) or (neuralgia* adj3 ciliar*) or horton* syndrome*).tw,kw,kf. (10042)
27 or/23-26 (148965)
28 transcutaneous electrical nerve stimulation/ (9542)
29 vagus nerve stimulation/ and (noninvasiv* or non invasiv* or less invasiv* or portab* or transcutaneous*).tw,kw,kf,dv. (2454)
30 (((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous* or cervical*) adj5 (vagal nerve* or vagus nerve*) adj5 stimulat*) or nVNS).tw,kw,kf,dv. (3291)
31 ((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous*) adj3 (neurostimulat* or neuromodulat*)).tw,kw,kf,dv. (4047)
32 (gammacore* or gamma core* or sapphire* or electrocore* or RSK medical* or cerbomed*).tw,kw,kf,dv. (7434)
33 or/28-32 (23632)
34 27 and 33 (1027)
35 (exp animal/ or nonhuman/) not exp human/ (11904193)
36 34 not 35 (992)
37 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11312595)
38 36 not 37 (767)
39 limit 38 to english language [Limit not valid in CDSR; records were retained] (725)
40 39 use emez (316)
41 22 or 40 (636)
42 41 use medall (256)
43 41 use coch (0)
44 41 use cctr (64)
45 41 use cleed (0)
46 41 use emez (316)
47 remove duplicates from 41 (397)

Economic Evidence Search

Search Date: September 13, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 6, 2023>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 36>, Ovid MEDLINE(R) ALL <1946 to September 12, 2023>

Search Strategy:

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1 exp Migraine Disorders/ (112454)
2 (migrain* or (sick adj headache*)).ti,ab,kf. (118769)
3 Cluster Headache/ (8912)
4 ((cluster* adj5 headache*) or (histamin* adj3 cephalgi*) or (neuralgia* adj3 ciliar*) or horton* syndrome*).ti,ab,kf. (10018)
5 or/1-4 (148465)
6 Transcutaneous Electric Nerve Stimulation/ (10813)
7 Vagus Nerve Stimulation/ and (noninvasiv* or non invasiv* or less invasiv* or portab* or transcutaneous*).ti,ab,kf. (2453)
8 (((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous* or cervical*) adj5 (vagal nerve* or vagus nerve*) adj5 stimulat*) or nVNS).ti,ab,kf. (3279)
9 ((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous*) adj3 (neurostimulat* or neuromodulat*)).ti,ab,kf. (3520)
10 (gammacore* or gamma core* or sapphire* or electrocore* or RSK medical* or cerbomed*).ti,ab,kf. (7089)
11 or/6-10 (24134)
12 5 and 11 (1021)
13 limit 12 to english language [Limit not valid in CDSR; records were retained] (978)
14 13 use coch,cleed (0)
15 economics/ (264763)
16 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1058380)
17 economics.fs. (470253)
18 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1290586)
19 exp "costs and cost analysis"/ (693097)
20 (cost or costs or costing or costly).ti. (334914)
21 cost effective*.ti,ab,kf. (455541)
22 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kf. (313326)
23 models, economic/ (16047)
24 markov chains/ or monte carlo method/ (108380)
25 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (68067)
26 (markov or markow or monte carlo).ti,ab,kf. (180773)
27 quality-adjusted life years/ (56201)
28 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (113047)
29 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (196623)
30 or/15-29 (3405844)
31 13 and 30 (56)
32 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6516503)
33 31 not 32 (55)
34 exp Animals/ not Humans/ (16348105)
35 33 not 34 (46)

36 35 use medall,cctr (22)
37 14 or 36 (22)
38 exp migraine/ (112454)
39 (migrain* or (sick adj headache*)).tw,kw,kf. (119267)
40 exp cluster headache/ (9709)
41 ((cluster* adj5 headache*) or (histamin* adj3 cephalgi*) or (neuralgia* adj3 ciliar*) or horton* syndrome*).tw,kw,kf. (10042)
42 or/38-41 (148965)
43 transcutaneous electrical nerve stimulation/ (9542)
44 vagus nerve stimulation/ and (noninvasiv* or non invasiv* or less invasiv* or portab* or transcutaneous*).tw,kw,kf,dv. (2454)
45 (((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous* or cervical*) adj5 (vagal nerve* or vagus nerve*) adj5 stimulat*) or nVNS).tw,kw,kf,dv. (3291)
46 ((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous*) adj3 (neurostimulat* or neuromodulat*)).tw,kw,kf,dv. (4047)
47 (gammacore* or gamma core* or sapphire* or electrocore* or RSK medical* or cerbomed*).tw,kw,kf,dv. (7434)
48 or/43-47 (23632)
49 42 and 48 (1027)
50 limit 49 to english language [Limit not valid in CDSR; records were retained] (985)
51 Economics/ (264763)
52 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (147856)
53 Economic Aspect/ or exp Economic Evaluation/ (556504)
54 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1310928)
55 exp "Cost"/ (693097)
56 (cost or costs or costing or costly).ti. (334914)
57 cost effective*.tw,kw,kf. (464370)
58 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kw,kf. (323007)
59 Monte Carlo Method/ (84168)
60 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (71471)
61 (markov or markow or monte carlo).tw,kw,kf. (184244)
62 Quality-Adjusted Life Years/ (56201)
63 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (116396)
64 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (217374)
65 or/51-64 (2925451)
66 50 and 65 (43)
67 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11312595)
68 66 not 67 (35)
69 (exp animal/ or nonhuman/) not exp human/ (11904193)
70 68 not 69 (35)
71 70 use emez (16)
72 37 or 71 (38)
73 72 use medall (16)
74 72 use emez (16)
75 72 use cctr (6)

76 72 use coch (0)
77 72 use cleed (0)
78 remove duplicates from 72 (30)

Grey Literature Search

Performed on: September 14 – 19, 2023

Websites searched:

Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services, Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Norwegian Institute of Public Health-Health Technology Assessments, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Sick Kids PEDE Database, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used:

cluster headache, migraine, gammacore, electrocore, nVNS, vagus, vagal, nerve stimulation, noninvasive, non invasive, sapphire, neurostimulation, neuromodulation, céphalées en grappes, nerf vague, nerf vagal
Clinical results (included in PRISMA): 6
Economic results (included in PRISMA): 4
Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 10
Ongoing clinical trials: 12

Search for Intervention-Related Health State Utilities

Search Date: September 27, 2023

Database searched: Ovid MEDLINE

Database segment: Ovid MEDLINE(R) ALL <1946 to September 26, 2023>

Search Strategy:

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1 exp Migraine Disorders/ (32052)
2 (migrain* or (sick adj headache*)).ti,ab,kf. (43156)
3 Cluster Headache/ (2929)
4 ((cluster* adj5 headache*) or (histamin* adj3 cephalgi*) or (neuralgia* adj3 ciliar*) or horton* syndrome*).ti,ab,kf. (3795)
5 or/1-4 (49848)
6 Transcutaneous Electric Nerve Stimulation/ (5655)
7 Vagus Nerve Stimulation/ and (noninvasiv* or non invasiv* or less invasiv* or portab* or transcutaneous*).ti,ab,kf. (555)
8 (((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous* or cervical*) adj5 (vagal nerve* or vagus nerve*) adj5 stimulat*) or nVNS).ti,ab,kf. (1067)
9 ((non invasiv* or noninvasiv* or less invasiv* or portab* or transcutaneous*) adj3 (neurostimulat* or neuromodulat*)).ti,ab,kf. (1167)
10 (gammacore* or gamma core* or sapphire* or electrocore* or RSK medical* or cerbomed*).ti,ab,kf. (3603)
11 or/6-10 (11117)
12 5 and 11 (297)
13 Quality-Adjusted Life Years/ (15840)
14 (quality adjusted or adjusted life year*).ti,ab,kf. (23885)
15 (qaly* or qald* or qale* or qtime*).ti,ab,kf. (14835)
16 (illness state$1 or health state$1).ti,ab,kf. (8497)
17 (hui or hui1 or hui2 or hui3).ti,ab,kf. (1999)
18 (multiattribute* or multi attribute*).ti,ab,kf. (1342)
19 (utility adj3 (score$1 or valu* or health* or cost* or measure* or disease* or mean or gain or gains or index*)).ti,ab,kf. (19694)
20 utilities.ti,ab,kf. (9544)
21 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eurqol5d or euro?qul or eur?qul5d or euro* quality of life or European qol).ti,ab,kf. (17667)
22 (euro* adj3 (5 d or 5d or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).ti,ab,kf. (6081)
23 (sf36* or sf 36* or sf thirtysix or sf thirty six).ti,ab,kf. (26826)
24 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (2397)
25 ((qol or hrqol or quality of life).ti. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improve* or declin* or reduc* or high* or low* or effect or effects of worse or score or scores or change$1 or impact$1 or impacted or deteriorate$)).ab. (45352)
26 Cost-Benefit Analysis/ and (cost effectiveness ratio* and (perspective* or life expectanc*)).ti,ab,kf. (5292)
27 *quality of life/ and (quality of life or qol).ti. (64530)
28 quality of life/ and ((quality of life or qol) adj3 (improve* or chang*)).ti,ab,kf. (37518)
29 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (15797)
30 quality of life/ and health-related quality of life.ti,ab,kf. (45466)
31 quality of life/ and ec.fs. (10876)
32 quality of life/ and (health adj3 status).ti,ab,kf. (11890)

33 (quality of life or qol).ti,ab,kf. and cost-benefit analysis/ (17045)
34 models, economic/ (11089)
35 or/13-34 (217275)
36 12 and 35 (12)
37 limit 36 to english language (12)

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool), Cluster Headache

Author, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Gaul et al, 2016[53] (PREVA)	Unclear[b]	Unclear[b]	High[c]	Unclear to high[d]	Unclear[e]	Low,[f] unclear[g]
Silberstein et al, 2016[51] (ACT1)	Low	Low	Low	Unclear[h]	Low	Low,[f] high[i]
Goadsby et al, 2018[52] (ACT2)	Low	Low	Unclear[j]	High[k]	High[l]	Low,[f] unclear[m]

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] Possible risk-of-bias levels: low, high, and unclear.

[b] No details provided on how randomized sequence was generated or if allocation was concealed.

[c] Study was open-label with no sham device. All outcomes were based on unblinded patient self-report and are therefore at risk of bias.

[d] An intention-to-treat population was used for outcomes related to the frequency of headache; however, this analysis excluded randomized participants who did not have 1 or more efficacy measures entered after randomization. Given the low numbers lost (excluded 6% nVNS and 2% controls), we rated risk of bias as unclear. We assessed the risk of bias for other outcomes (i.e., acute medication use, quality of life) to be high because they were evaluated only among people with measurable observations across the respective study phases (modified intention-to-treat), with little information provided about who was excluded from these analyses.

[e] Data for some negative outcomes were not clearly reported in the publication (i.e., pain relief and duration of headache attacks), and adverse event outcomes were not reported separately for the randomized vs. the extension phases of the study, as with other outcomes.

[f] One of the study authors was employed by the manufacturer of the device, and the study was funded by the manufacturer.

[g] Additional secondary outcome measures were included in the published study that were not listed in the protocol (ClinicalTrials.gov NCT01701245): ≥ 50% response rate, acute medication use, and duration of attacks.

[h] Analysis did not include all people randomized to the study – only those who treated 1 or more attacks. A detailed flow chart was included, and imputation methods for missing data were reported, but the total number of discontinuations was high and unbalanced (19% nVNS, 10% control). Most unbalanced losses were due to no cluster headache or cluster headache ended, so we assessed the risk of bias as unclear.

[i] We rated post-hoc analyses (i.e., responders or pain free for ≥ 50% of treated attacks) as being at high risk of bias. Other exploratory analyses were said to be prespecified and were not assessed as being at high risk of bias.

[j] Patients and assessors were blinded, but study trainers were unblinded and may have introduced bias into the study.

[k] Analyses did not include all people randomized to the study – only those who treated 1 or more attacks. The number of overall discontinuations or exclusions from analysis was high and unbalanced (10% nVNS and 27% controls). No description was provided of the imputation of missing data.

[l] Several outcomes listed in the protocol (ClinicalTrials.gov NCT01958125) were not reported or listed in any publication (i.e., EQ-5D, rescue medication usage, change in disability scale).

[m] Multiple additional outcomes and exploratory analyses included in the publication (i.e., responder at 30 minutes, pain intensity, ≥ 50% response for pain-free, ≥ 50% response for pain relief) were not listed in the protocol. It was unclear if these were post hoc or planned analyses.

Table A2: Risk of Bias[a] Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool), Migraine

Author, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Silberstein et al, 2016[56] (EVENT)	Low	Unclear[b]	Unclear[c]	Unclear[d]	Unclear[e]	High,[f] low[g]
Tassorelli et al, 2018[55] (PRESTO) *Martelletti et al, 2018[64]*	Low	Unclear[b]	Unclear[c]	Low to high[h]	Unclear[i]	Unclear to high,[j] low[g]
Chaudhry et al, 2019[59]	Low	Unclear[b]	Unclear[c]	High[k]	Low	Low
Diener et al, 2019[57] (PREMIUM)	Low	Low	Unclear[c]	High[l]	Unclear[m]	Unclear,[n] low[g]
Najib et al, 2022[58] (PREMIUM II)	Low	Low	Unclear[c]	High[o]	Low	Low,[g] unclear[p]

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

[a] Possible risk-of-bias levels: low, high, and unclear.

[b] No details were provided about if or how allocation was concealed.

[c] Study participants, investigators, and coordinators were blinded, but study trainers were unblinded and may have introduced bias into the study.

[d] The intention-to-treat population included only people who provided data for each outcome; there was high loss to follow-up (13% nVNS, 14% controls).

[e] Quality-of-life outcomes listed in the ClinicalTrials.gov protocol were not reported in any publication.

[f] High risk of bias for the outcome of treatment response because this was a post hoc analysis.

[g] The study was funded by the device manufacturer and included authors with manufacturer affiliations.

[h] The intention-to-treat population required at least 1 attack to be treated, but the number of exclusions for this reason was low, and overall loss to follow-up was low. The outcome of ≥ 50% responder rates were at high risk of bias because analyses excluded those who treated only 1 attack, and the number included was unbalanced between groups. Sustained response rates were at high risk of bias because analyses excluded those who did not achieve initial response and did not match the online protocol definition.

[i] Quality-of-life outcomes listed in the ClinicalTrials.gov protocol (EQ-5D, HIT-6) were not reported in any publication.

[j] Several outcomes that were not stated in the online protocol were reported in the publication, and it was unclear whether they were prespecified or post hoc. Outcomes clearly labelled as post hoc analyses (i.e., consistency in pain freedom, pain intensity) were assessed as being at very high risk of bias. Pain intensity was reported as a post hoc analysis in the initial publication and using other effect measures in subsequent papers. Data reported in the subsequent publication by Martelletti et al[64] were assessed as being at unclear risk of bias because it was not stated whether additional findings were part of preplanned or post hoc analyses.

[k] People who had issues with the device or certain side effects were excluded from the analysis. No information was provided about additional loss to follow-up or patient flow, and no information was provided about planned statistical analyses for the accounting of missing data.

[l] The intention-to-treat analysis required at least 1 treatment to be included in study, but exclusion for this was low and similar between groups. Overall discontinuation was high (18% nVNS, 24% control).

[m] Quality-of-life outcomes listed in the ClinicalTrials.gov protocol (HIT-6, MIDAS, EQ-5D) were not reported in any publication.

[n] Additional analyses were reported in the publication that were not in the ClinicalTrials.gov protocol (i.e., ≥ 50% responder rate for headache days and acute medication days and perception of device).

[o] The primary analysis was not an intention-to-treat population; it was limited to those with ≥ 67% adherence to treatment each week and in the double-blind period for > 70 days. There was substantial loss to follow-up (nVNS 50%, controls 51%).

[p] Additional outcomes were not listed in the ClinicalTrials.gov protocol (i.e., HIT-6, MIDAS, satisfaction) but included in the publication.

Table A3: GRADE Evidence Profile for the Comparison of nVNS and Control, Acute Use, Cluster Headache

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Pain relief: response							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations[b]	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Pain relief: response in 50% or more of attacks							
2 (RCTs)	Very serious limitations (−2)[a]	No serious limitations[d]	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⨁ Very low
Pain relief: sustained treatment response							
1 (RCT)	No serious limitations	No serious limitations[f]	No serious limitations	Very serious limitations (−2)[g]	Undetected	None	⨁⨁ Low
Pain freedom							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[f]	No serious limitations	Serious limitations (−1)[h]	Undetected	None	⨁⨁ Low
Pain freedom in 50% or more of attacks							
2 (RCTs)	Very serious limitations (−2)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[i]	Undetected	None	⨁ Very low
Headache intensity							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations[b]	Serious limitations (−1)[j]	Undetected	None	⨁⨁ Low
Duration of headache attack							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[f]	No serious limitations	Serious limitations (−1)[k]	Undetected	None	⨁⨁ Low
Acute medication use							
1 (RCT)	No serious limitations	No serious limitations[f]	No serious limitations	Serious limitations (−1)[l]	Undetected	None	⨁⨁⨁ Moderate
≥ 1 Adverse event							
2 (RCTs)	Serious limitations (−1)[a]	Serious limitations (−1)	No serious limitations[m]	Serious limitations (−1)[n]	Undetected	None	⨁ Very low
≥ 1 Severe adverse event							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations[m]	Serious limitations (−2)[o]	Undetected	None	⨁ Very low
≥ 1 Device-related adverse event							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations[m]	Serious limitations (−1)[n]	Undetected	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; nVNS, noninvasive vagus nerve stimulation; RCT, randomized controlled trial.

[a] See Table A1.

[b] Outcome measured differently by the 2 studies, but not downgraded.

[c] Small sample sizes and very wide confidence intervals that crossed no effect in both studies.

[d] Moderate inconsistency, but not downgraded.

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[e] Confidence intervals were very wide and crossed no effect or a moderate decrease in response.

[f] Inconsistency could not be assessed because only 1 study contributed to the outcome.

[g] Only 1 study included, with a very small sample size and wide confidence intervals that included a very large effect and a small, not clinically meaningful effect (absolute difference 1%). Given that no risk of bias was present, greater weight was placed on the severe imprecision, downgrading 2 levels.

[h] Very small sample size with a confidence interval that crossed no effect ($P > .05$).

[i] Extremely wide confidence intervals that included a very large increase in response and a decrease in response.

[j] Very small sample sizes in both studies, with confidence intervals that included no effect in both studies.

[k] Small sample size with a very wide confidence interval that included a large reduction in duration and a 6-minute increase in duration.

[l] Small sample size with a confidence interval that crossed no effect.

[m] No description of how adverse events and device-related adverse events were predefined.

[n] Wide confidence interval that crossed no effect.

[o] Extremely wide confidence interval that included very large harm and a reduction in adverse events. Further downgraded due to a very low number of events.

Table A4: GRADE Evidence Profile for the Comparison of nVNS and Control, Prevention, Cluster Headache

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Frequency – attacks per week							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[c]	Undecected	None	⨁⨁ Low
Frequency – response							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⨁⨁ Low
Severity or duration of headache attacks							
1 (RCT)	Very serious limitations (−2)[a]	Unable to assess[e]	Unable to assess[e]	Unable to assess[e]	Unable to assess[e]	Unable to assess[e]	Unable to assess[e]
Acute medication use							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations[f]	Serious limitations (−1)[d]	Undetected	None	⨁⨁ Low
Adverse events							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[g]	Undetected	None	⨁⨁ Low
Quality of life, EQ-5D-3L							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[h]	Undetected	None	⨁⨁ Low
Quality of life, HIT-6							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations	Very serious limitations (−2)[i]	Undetected	None	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HIT-6, 6-item Headache Impact Test; nVNS, noninvasive vagus nerve stimulation; RCT, randomized controlled trial.

[a] See Table A1.

[b] Inconsistency could not be assessed because only 1 RCT contributed to the analysis.

[c] A single study with a small sample size; very wide confidence intervals ranged from little or no difference to a very large reduction.

[d] A single study with a small sample size; very wide confidence intervals.

[e] Authors did not report data, statistics, *P* values or other information required for GRADE analysis.

[f] Limited information about how this was measured and how it interacted with acute use of the nVNS device, but not downgraded further.

[g] Confidence interval included a large increase in adverse events and a reduction.

[h] Single study with a small sample size. Confidence interval crossed the threshold of a minimally important difference of 0.074.

[i] Insufficient data provided to assess variance around the effect estimate or statistical significance.

Table A5: GRADE Evidence Profile for the Comparison of nVNS and Control, Acute Treatment, Migraine

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Pain relief: response							
1 (RCT)	No serious limitations[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁⨁ Moderate
Pain relief: response in 50% or more of attacks							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⨁⨁ Low
Pain relief: sustained treatment response							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⨁⨁ Low
Pain freedom							
1 (RCT)	No serious limitations[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[f]	Undetected	None	⨁⨁⨁ Moderate
Pain freedom in 50% or more of attacks							
1 (RCT)	Very serious limitations (−2)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[g]	Undetected	None	⨁ Very low
Sustained pain freedom							
1 (RCT)	Very serious limitations (−2)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[h]	Undetected	None	⨁ Very low
Headache intensity							
1 (RCT)	Very serious limitations (−2)[a]	No serious limitations[a]	No serious limitations	Serious limitations (−1)[i]	Undetected	None	⨁ Very low
Acute medication use							
1 (RCT)	No serious limitations[a]	No serious limitations[b]	Serious limitations (−1)[j]	Serious limitations (−1)[k]	Undetection	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; nVNS, noninvasive vagus nerve stimulation; RCT, randomized controlled trial.

[a] See Table A1.

[b] Only 1 RCT contributed to the assessment.

[c] Small sample size, with a very wide confidence interval ranging from a very small and not clinically meaningful increase (1% absolute risk increase, 3% relative increase) to a very large benefit.

[d] Small sample size, with a very wide confidence interval ranging from a very small and not clinically meaningful increase (2% absolute risk increase, 4% relative increase) to a very large benefit.

[e] Small sample size with a confidence interval that included a meaningful decrease and an increase in response.

[f] Small sample size with a wide confidence interval that crossed no effect in treatment.

[g] Small sample size with a very wide confidence interval.

[h] Small sample size that crossed no effect in treatment.

[i] Small sample size; no variance was provided to appropriately assess imprecision.

[j] It was unclear how this was defined, or the measures. Patients were instructed not to take medication for 120 minutes after treatment, and this was unlikely to represent true practice.

[k] Small sample size with a confidence interval that crossed no effect ($P > .05$); insufficient data to assess the degree of variance around the effect estimate.

Table A6: GRADE Evidence Profile for the Comparison of nVNS and Control, Prevention, Migraine

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Migraine days							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low
Headache days							
4 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Response – migraine days							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⨁⨁ Low
Response – headache days							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⨁⨁ Low
Acute medication use							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[f]	Undetected	None	⨁⨁ Low
≥ 1 Adverse event							
3 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations[g]	Serious limitations (−1)[h]	Undetected	None	⨁⨁ Low
≥ 1 Severe adverse event							
3 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations[g]	Serious limitations (−2)[i]	Undetected	None	⨁ Very low
≥ 1 Device-related adverse event							
3 (RCTs)	Serious limitations (−1)[a]	Serious limitations (−1)	No serious limitations[g]	Serious limitations (−1)[j]	Undetected	None	⨁ Very low
Quality of life, HIT-6							
1 (RCT)	Very serious limitations (−2)[a]	No serious limitations[k]	No serious limitations	Serious limitations (−1)[l]	Undetected	None	⨁ Very low
Quality of life, MIDAS							
1 (RCT)	Very serious limitations (−2)[a]	No serious limitations[m]	No serious limitations[n]	Serious limitations (−1)[o]	Undetected	None	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; nVNS, noninvasive vagus nerve stimulation; RCT, randomized controlled trial.

[a] See Table A1.

[b] Confidence intervals crossed no effect in both studies; no reporting of variance around the effect estimates, so we were unable to assess the degree of imprecision.

[c] Results were not statistically significant in any of the trials, indicating that confidence intervals crossed no effect. The degree of imprecision around estimates could not be determined for 3 of the 4 studies, because variance around the summary estimates was not provided. One study included variance, but results were very imprecise and based on a very small sample size.

[d] The confidence interval was wide and crossed no effect in the larger study with lower risk of bias. The second trial was very underpowered and approached little to no difference in the lower confidence interval based on *P* values.

[e] Both studies had very wide confidence intervals that included a large benefit and harm. The overall sample size was low.

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[f] Both studies crossed no effect in treatment (*P* > .05); however, the degree of imprecision could not be assessed because variance around the effect estimates was not reported and could not be calculated. The sample size was small for both studies.

[g] It was unclear how adverse events, serious adverse events, or device-related adverse events were defined by study, but we did not downgrade.

[h] Confidence intervals included a benefit and a 3% absolute increase in adverse events.

[i] The total number of events was very low in both arms. The confidence intervals were very wide and crossed no effect or an increase in adverse events.

[j] Confidence intervals were very wide, crossing a large reduction in adverse events as well as harm (absolute and relative effects).

[k] Only 1 study contributed to the analysis.

[l] Very small sample size; insufficient data to assess variance around the effect estimate.

[m] Studies reported this outcome measure differently, but we did not downgrade.

[n] One study found little to no difference in effect, and the other found a large reduction.

[o] Very small sample size. We were unable to assess variance around the effect estimate, although confidence intervals approached no effect (*P* = .05).

Appendix 3: Selected Excluded Studies – Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Primary studies	
Trimboli M, Al-Kaisy A, Andreou AP, Murphy M, Lambru G. Non-invasive vagus nerve stimulation for the management of refractory primary chronic headaches: a real-world experience. Cephalalgia. 2018;38(7):1276-85.	No active comparator arm
Simmonds L, Lagrata S, Stubberud A, Cheema S, Tronvik E, Matharu M, et al. An open-label observational study and meta-analysis of non-invasive vagus nerve stimulation in medically refractory chronic cluster headache. Front Neurol. 2023;14:1100426.	No active comparator arm
Kinfe TM, Pintea B, Muhammad S, Zaremba S, Roeske S, Simon BJ, et al. Cervical non-invasive vagus nerve stimulation (nVNS) for preventive and acute treatment of episodic and chronic migraine and migraine-associated sleep disturbance: a prospective observational cohort study. J Headache Pain. 2015;16:101.	No active comparator arm
Grazzi L, Egeo G, Calhoun AH, McClure CK, Liebler E, Barbanti P. Non-invasive vagus nerve stimulation (nVNS) as mini-prophylaxis for menstrual/menstrually related migraine: an open-label study. J Headache Pain. 2016;17(1):91.	No active comparator arm
Nesbitt AD, Marin JC, Tompkins E, Ruttledge MH, Goadsby PJ. Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology. 2015; 84(12):1249-53.	No active comparator arm
Mwamburi M, Liebler EJ, Staats PS. Patient experience with non-invasive vagus nerve stimulator: gammaCore patient registry. Am J Manag Care. 2020;26(1 Suppl):S15-S19.	No active comparator arm
de Coo IF, Marin JC, Silberstein SD, Friedman DI, Gaul C, McClure CK, et al. Differential efficacy of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a meta-analysis. Cephalalgia. 2019;39(8):967-77.	Not a systematic review or primary study
Marin J, Giffin N, Consiglio E, McClure C, Liebler E, Davies B. Non-invasive vagus nerve stimulation for treatment of cluster headache: early UK clinical experience. J Headache Pain. 2018;19(1):114.	No active comparator arm
Grazzi L, Egeo G, Liebler E, Padovan AM, Barbanti P. Non-invasive vagus nerve stimulation (nVNS) as symptomatic treatment of migraine in young patients: a preliminary safety study. Neurol Sci. 2017;38(Suppl 1):197-9.	No active comparator arm
Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. Cephalalgia. 2014;34(12):986-93.	No active comparator arm
Barbanti P, Grazzi L, Egeo G, Padovan AM, Liebler E, Bussone G. Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. J Headache Pain. 2015;16:61.	No active comparator arm
Systematic reviews and health technology assessments	
Song D, Li P, Wang Y, Cao J. Noninvasive vagus nerve stimulation for migraine: a systematic review and meta-analysis of randomized controlled trials. Front Neurol. 2023;14:1190062.	Population (migraine only), no GRADE assessment, not all outcomes
May A, Evers S, Goadsby PJ, Leone M, Manzoni GC, Pascual J, et al. European Academy of Neurology guidelines on the treatment of cluster headache. Eur J Neurol. 2023;30(10):2955-79.	Intervention (preventive use only)
Chen YL, Chen Q, Li LW, Hua C, Zhang XY, Zheng H. Non-invasive brain stimulation treatments for migraine prophylaxis: a network meta-analysis of randomized controlled trials. Acta Neurol Belg. 2023;123(4):1481-93.	Wrong study design (network meta-analysis)
Cheng YC, Zeng BY, Hung CM, Su KP, Wu YC, Tu YK, et al. Effectiveness and acceptability of noninvasive brain and nerve stimulation techniques for migraine prophylaxis: a network meta-analysis of randomized controlled trials. J Headache Pain. 2022;23(1):28.	Wrong study design (network meta-analysis)
Clark O, Mahjoub A, Osman N, Surmava AM, Jan S, Lagman-Bartolome AM. Non-invasive neuromodulation in the acute treatment of migraine: a systematic review and meta-analysis of randomized controlled trials. Neurol Sci. 2022;43(1):153-65.	Intervention (combined with other neuromodulation); population (only acute migraine)

Citation	Primary reason for exclusion
Medrea I, Christie S, Tepper SJ, Thavorn K, Hutton B. Network meta-analysis of therapies for cluster headache: effects of acute therapies for episodic and chronic cluster. Headache. 2022;62(4):482-511.	Wrong study design (network meta-analysis)
VanderPluym JH, Halker Singh RB, Urtecho M, Morrow AS, Nayfeh T, Torres Roldan VD, et al. Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. JAMA. 2021;325(23):2357-69.	Population (only acute episodic migraine)
Lai YH, Huang YC, Huang LT, Chen RM, Chen C. Cervical noninvasive vagus nerve stimulation for migraine and cluster headache: a systematic review and meta-analysis. Neuromodulation. 2020;23(6):721-31.	Population (combined migraine and cluster headache)
Moisset X, Pereira B, Ciampi de Andrade D, Fontaine D, Lanteri-Minet M, Mawet J. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. J Headache Pain. 2020;21(1):142.	Intervention not clearly specified
Halker Singh RB, VanderPluym JH, Morrow AS, Urtecho M, Nayfeh T, Torres Roldan VD, et al Acute treatments for episodic migraine. Comparative effectiveness review no. 239. AHRQ Publication No. 21-EHC009. Rockville (MD): Agency for Healthcare Research and Quality; December 2020.	Intervention (nVNS not clearly specified); population (only acute episodic migraine)
National Institute for Health and Care Excellence. GammaCore for cluster headache. Medical Technologies Guidance [MTG46]. 2019.	Critique of industry submission
Chaudry FPA, Klem HE, Næss GE, Castenada MG, Movik E, Brurberg KG. Transcutaneous non-invasive vagus nerve stimulation (gammaCore) for the treatment of cluster headache: a single technology assessment. Oslo: Norwegian Institute of Public Health; 2023.	Critique of industry submission

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; nVNS, noninvasive vagus nerve stimulation.

Appendix 4: Exclusion Criteria From Included Studies

Table A7: Exclusion Criteria From Included Studies

Author, year	Exclusion criteria (quoted or paraquoted by individual studies)
Cluster headache	
Silberstein et al, 2016[51] (ACT1)	• Pregnant or lactating • History of aneurysm, intracranial hemorrhage, brain tumours, significant head trauma, prolonged QT interval, arrhythmia, ventricular tachycardia or fibrillation, syncope, or seizure; structural intracranial or cervical vascular lesions; cardiovascular disease; uncontrolled hypertension; abnormal baseline electrocardiogram • Significant pain disorder • Botulinum toxin injections in the past 3 mo; nerve blocks in the past 1 mo • Previous cluster headache surgery, bilateral or right cervical vagotomy, carotid endarterectomy, or right vascular neck surgery; electrical device implantation • Current use of prophylactic medications for indications other than cluster headache
Goadsby et al, 2018[52] (ACT2)	• Episodice cluster headache and not in a bout at the time of screening • Pregnant or nursing • Need to begin treatment with oral or injectable steroids; use of medication that might have interfered with the study • Lesion, dysesthesia, previous surgery, or abnormal anatomy at the treatment site; history of cranial aneurysm, intracranial hemorrhage, brain tumour, significant head trauma, carotid endarterectomy, vascular neck surgery, or cervical vagotomy • Secondary headache or other significant pain condition • Abnormal baseline electrocardiogram; known or suspected atherosclerotic cardiovascular disease, severe carotid artery disease, congestive heart failure, known severe coronary artery disease, or recent myocardial infarction; uncontrolled high blood pressure • Recent or repeated history of syncope or seizures • Implanted electrical and/or neurostimulator device, metal cervical spine hardware, or metallic apparatus near the stimulation site • History of substance abuse, addiction, or headache medication overuse or a psychiatric or cognitive condition that may have interfered with the study
Tassorelli et al, 2018[55] (PRESTO)	• History of secondary headache, aneurysm, intracranial hemorrhage, brain tumours, significant head trauma, substance abuse, addiction, syncope, or seizure • Significant pain disorder • Cardiovascular or cerebrovascular disease; uncontrolled hypertension • Psychiatric or cognitive disorders • Pregnancy • Requiring oral or injectable steroids; botulinum toxin injections in the past 6 mo; head or neck nerve blocks in the past 2 mo; previous migraine prevention surgery • Cervical vagotomy, electrical device, or metal cervical spine hardware implantation • Current use of opioids for > 2 d per mo; current use of simple analgesics or nonsteroidal anti-inflammatory drugs for > 15 d per mo; current use of triptans, ergots, or combined analgesics for > 10 d per mo; initiation of preventive migraine medications in the past 2 mo

Author, year	Exclusion criteria (quoted or paraquoted by individual studies)
Migraine	
Gaul et al, 2016[53] (PREVA)	• Change in prophylactic medication type or dosage < 1 mo before enrolment • History of intracranial or carotid aneurysm or hemorrhage; brain tumours or lesions; signficant head trauma, surgery, or abnormal anatomy at the nVNS treatment site; history of syncope or seizures • Known or suspected cardiac or cardiovascular disease • Implantatation with electrical or neurostimulation devices; history of carotid endarterectomy or vascular neck surgery; implantation with metallic hardware
Silberstein et al, 2016[56] (EVENT)	• History of aneurysm, intracranial hemorrhage, brain tumour, or head trauma; a lesion, dysesthesia, previous surgery, or abnormal anatomy at the treatment site • Cardiovascular disease; uncontrolled hypertension; abnormal electrocardiogram results; recent myocardial infarction • Implanted electrical or neurostimulator device; a metallic implant or metal cervical spine hardware near the stimulation site • Previous surgery for migraine prevention; onabotulinumtoxin A injections for migraine prevention within 6 mo; prophylactic migraine medication within 30 d
Chaudhry et al, 2019[59]	• Concomitant neuropsychiatric comorbidity not adequately classified and/or requiring specific diagnosis or treatment • Pregnancy • Previously performed invasive, noninvasive, and ablative procedures • Intracranial and cervical pathologies • Medication overuse headache
Diener et al, 2019[57] (PREMIUM)	• Chronic migraine diagnosis; previous diagnosis of medication overuse headache that had reverted to episodic migraine in the past 6 mo • Medical condition requiring oral or injectable steroids • History of secondary headache, aneurysm, intracranial haemorrhage, brain tumours, significant head trauma, substance abuse, addiction, syncope, or seizure • Structural abnormality, pain, or metal cervical spine hardware implantation near treatment site • Significant pain disorder • Cardiovascular or cerebrovascular disease; abnormal electrocardiogram; uncontrolled hypertension • Previous migraine prevention surgery, cervical vagotomy, or electrical or neurostimulator device implantation • Psychiatric or cognitive disorders; pregnancy • Botulinum toxin injections in the past 6 mo; head or neck nerve blocks in the past 2 mo; failure of at least 3 classes of migraine prevention drugs; opioid use; marijuana use; simple analgesic or nonsteroidal anti-inflammatory drug use (> 15 d per mo); or triptan, ergot, or combined analgesic use (> 10 d per mo) • Use of preventive migraine treatments at or within 30 d of baseline

Author, year	Exclusion criteria (quoted or paraquoted by individual studies)
Najib et al, 2022[58] (PREMIUM II)	• On 2 or more preventive therapies, injections of onabotulinumtoxin A or calcitonin gene-related peptide–targeting monoclonal antibody drugs within the last 6 mo • Takes simple analgesics or nonsteroidal anti-inflammatory drugs > 15 d per mo or triptans, ergots, or combined analgesics > 10 d per mo; prescription opioids more than 2 d per mo • Surgery for migraine prevention; undergone nerve block in head or neck within the last 3 mo • Medication overuse headache that had reverted to migraine, history of secondary headache disorder • History of intracranial aneurysm, intracranial hemorrhage, brain tumour, or significant head trauma • Structural abnormality or pain at the nVNS treatment site; previous cervical vagotomy; implanted with an electrical and/or neurostimulator device or metal cervical spine hardware or has a metallic implant near the nVNS stimulation site • Other significant pain problem • Severe cardiac disease, cerebrovascular disease, abnormal electrocardiogram within the last year; uncontrolled high blood pressure; history of syncope, seizure • History of substance abuse or addiction; currently using marijuana • Pregnant or thinking of becoming pregnant • Psychiatric or cognitive disorder and/or behavioural problems that may interfere with the study

Abbreviation: nVNS, noninvasive vagus nerve stimulation.

Appendix 5: Additional Analyses

Table A8: Proportion of Treated Attacks That Achieved Pain-Free Status in 15 Minutes, nVNS vs. Control, Acute Treatment, Cluster Headache

Author, year (study)	Subtype	Attacks, nVNS/control, n	Attacks, %		OR (95% CI)[a]	*P*[a]
			nVNS	Control		
Goadsby et al, 2018[52] (ACT2)	Overall	495/400	13.5	11.5	1.22 (0.42–3.51)	.71
	Episodic	101/81	47.5	6.2	9.19 (1.77–47.8)	< .01
	Chronic	394/319	4.8	12.9	0.41 (0.13–1.3)	.13

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation; OR, odds ratio.

[a] From adjusted model, adjusting for site in the overall and chronic cohorts, but not the episodic cohort.

Table A9: Response to Treatment – Post Hoc Response Thresholds, nVNS vs. Standard of Care, Prevention, Cluster Headache

Author, year (study)	Participants, nVNS/control, n	Response threshold (% reduction in mean number of attacks per week)	Response, %[a]		*P*
			nVNS	Control	
Gaul et al, 2017[54] (PREVA)	37/47	≥ 25%	76	23	< .001
		≥ 75%	49	9	< .009
		≥ 100%	8	0	NR

Abbreviation: NR, not reported; nVNS, non-invasive vagus nerve stimulation

[a] Measured only among people who had efficacy data for all phases of the study.

Table A10: Proportion of All Attacks Achieving Pain Relief, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time, min	Total attacks, nVNS/control, n	Percent (95% CI)		*P*[a]
			nVNS	Control	
Martelletti et al, 2018[64] (PRESTO)	120	373/347	35.2 (28.9–42.2)	24.4 (18.8–31.0)	.018
	60		29.4 (23.9–35.7)	20.3 (15.4–26.4)	.025
	30		21.4 (16.2–27.8)	16 (11.5–21.7)	.15

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation.
[a] Adjusted for pain score at baseline, use of preventive therapies, and presence of aura.

Table A11: Sustained Pain Relief for All Treated Attacks, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time, h	Participants, nVNS/control, n	Percent		*P*[a]
			nVNS	Control	
Martelletti et al, 2018[64] (PRESTO)	24	138/99	80.9	80.3	.92
	48		74.1	72.1	.78

Abbreviations: nVNS, noninvasive vagus nerve stimulation.
[a] Calculated from data reported in the study.

Table A12: Percentage of All Attacks Achieving Pain Freedom, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time, min	Total attacks, nVNS/control, n	Percent (95% CI)		*P*[a]
			nVNS	Control	
Martelletti et al, 2018[64] (PRESTO)	120	373/347	22.9 (18.0–28.6)	14.8 (10.5–20.5)	.13
	60		16.3 (12.1–21.5)	8.6 (5.6–12.9)	.005
	30		8.6 (5.6–12.9)	5.5 (3.2–9.3)	.13

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation.
[a] Study models adjusted for pain score at baseline, use of preventive therapies, and indicator or presence of aura.

Table A13: Sustained Pain Freedom for All Treated Attacks, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time, h	Participants, nVNS/control, n	Percent		*P*
			nVNS	Control	
Martelletti et al, 2018[64] (PRESTO)	24	93/66	79	83.7	.53
	48		65.7	71.2	.54

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation.

Table A14: Mean Change in Pain Score From Baseline to Follow-up for All Treated Attacks, nVNS vs. Control, Acute Treatment, Migraine

Author, year (study)	Time, min	Mean change from baseline		*P*
		nVNS	Control	
Martelletti et al, 2018[64] (PRESTO)	120	–0.5	–0.28	.057
	60	–0.42	–0.22	.029
	30	–0.33	–0.2	.11

Abbreviations: CI, confidence interval; nVNS, noninvasive vagus nerve stimulation.

Appendix 6: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A15: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of nVNS

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment[a]
Morris et al, 2016,[81] Germany	Partially (cluster headache, refractory patients only)	Yes	Unclear (UK perspective presented as a paragraph)	Yes, German statutory health insurance	Yes	NA, short time horizon	Yes	No (unclear how costs and outcomes differed for exclusively refractory patients; UK costs and utilities not specified)	Partially applicable
Mwamburi et al, 2017,[82] United States	Yes (cluster headache)	Yes	No	Partially (payer perspective; not specified which payer)	Yes	NA, short time horizon	Yes	No (costs not itemized)	Partially applicable
Mwamburi et al, 2018,[83] United States	Yes (migraine)	Yes	No	Partially (payer perspective; not specified which payer)	Yes	NA, short time horizon	Yes	No	Partially applicable
NICE medical technologies guidance, 2019,[30,b] and supplementary materials	Yes (cluster headache)	Yes	Yes (UK National Health Service)	Yes (UK National Health Service)	Yes	Partially (costs discounted at 3.5%; uncertainty surrounding why costs discounted at 1 year)	No (cost only)	No	Partially applicable
Norwegian Institute of Public Health HTA, 2023[65,b] (manufacturer-submitted cost–utility analysis)	Yes (cluster headache)	Yes	Partially (Norway)	Yes (Norwegian health care)	Yes	NA, short time horizon	Yes	No	Partially applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

Abbreviations: HTA, health technology assessment; NHS; National Health Service, UK, United Kingdom.

[a] Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

[b] Grey literature and secondary evidence.

Table A16: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of nVNS

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[b]
Morris et al, 2016,[81] Germany	Partially	Unclear	Partially	Partially	Yes	Unclear (costs unspecified for UK perspective)	Unclear	Unclear	Yes	Partially	Yes (some authors are employees and stockholders of the intervention manufacturer)	Potentially serious limitations
Mwamburi et al, 2017,[82] United States	Partially	Unclear	Partially	Yes	Partially	Unclear (itemized costs not reported – data availability issue)	Unclear	Unclear	Yes	Yes	Yes (study funded by manufacturer, some authors are employees and stockholders of intervention manufacturer)	Potentially serious limitations
Mwamburi et al, 2018,[83] United States	Partially	Unclear	Partially	Yes	Partially	Yes	Unclear	Unclear	Yes	Partially	Yes (study funded by manufacturer, some authors are employees and stockholders of intervention manufacturer)	Potentially serious limitations

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[b]
NICE medical technologies guidance, 2019,[30,c] and supplementary materials (manufacturer-submitted economic model)	Partially	Unclear	Partially	NA (costing study only)	NA (costing study only)	Yes	Unclear	Unclear	Partially (incremental costs)	Yes	NA (review of evidence submitted by manufacturer)	NA
Norwegian Institute of Public Health HTA, 2023[65,c] (manufacturer-submitted cost–utility analysis)	Partially	Unclear	Partially	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	NA (review of cost–utility model submitted by manufacturer)	NA

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a] Clinical inputs include relative treatment effects, natural history, and utilities.

[b] Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

[c] Grey literature and secondary evidence.

Appendix 7: Productivity Loss Calculations

Table A17: Productivity Loss Calculations, Cluster Headache

Calculation	Productivity loss per 4 wk, societal perspective	Reference
Productivity loss (societal perspective only), standard care arm	$653.75	Calculated based on Ford et al[101] and average hourly wage in Ontario[102]
Productivity loss (societal perspective only), nVNS arm	$503.21	Calculated based on Ford et al,[101] average hourly wage in Ontario,[102] and reduction in number of cluster headache attacks based on the PREVA RCT[53]
Mean difference between arms	$133.54	Calculated based on Ford et al[101] and average hourly wage in Ontario[102]

Abbreviations: nVNS, noninvasive vagus nerve stimulation; RCT, randomized, controlled trial.

Table A18: Productivity Loss Calculations, Migraine

Calculation	Productivity loss per mo, societal perspective	Reference
Productivity loss (societal perspective only), standard care arm	$351.20	Calculated based on Lambert et al[107] and average hourly wage in Ontario[102]
Productivity loss (societal perspective only), nVNS arm	$295.19	Calculated based on Lambert et al,[107] average hourly wage in Ontario,[102] and reduction in number of migraine attacks based on the PREMIUM RCT[57]
Mean difference between arms	$56.01	Calculated based on Lambert et al[107] and average hourly wage in Ontario[102]

Abbreviations: nVNS, noninvasive vagus nerve stimulation; RCT, randomized, controlled trial.

Appendix 8: Letter of Information

Ontario Health is conducting a review of noninvasive vagus nerve stimulation for cluster headaches or migraines. The purpose is to better understand how this intervention can be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers of those who have been diagnosed with cluster headaches or migraines and who may or may not have used noninvasive vagus nerve stimulation.

What Do You Need From Me

- Willingness to share your story
- 30–40 minutes of your time for a phone interview
- Permission to audio- (not video-) record the interview

What Your Participation Involves

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 30–40 minutes. It will be held over the telephone. With your permission, the interview will be audiotaped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions, or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

Confidentiality

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

If you are sending us personal information by email, please be aware that electronic communication is not always secure and can be vulnerable to interception.

Risks to Participation

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

If you are interested, please contact us.

Appendix 9: Interview Guide

Consent to Record

I would like your permission to have an audio recording of this conversation so I can use your direct quotes and other information from this conversation to make a case for the decision makers. Your name or any other identifiers will not be placed in the report or the presentation and your privacy and your confidentiality will be protected. Do I have your permission to audio record this conversation?

Explanation of Health Technology Assessments

What I'm doing is called a health technology assessment. This is where we review different technologies or interventions to be publicly funded. There are 3 main components. The first one is a clinical review; this is where we speak to clinical experts and look at the research around the technology. The second section is the economic review. This is where we look at the cost of technology in the healthcare system. And the third section, which is what you're taking part in, is patient preferences and values. This is where we speak to patients or caregivers about their lived experience with the condition the technology addresses and ask about their experience with the technology or their opinion on the technology if they haven't used it.

Once we gathered our evidence, we develop a report and presentation to a committee called the Ontario Health Technology Advisory committee. This committee based on the evidence we prepare for them makes a recommendation to publicly fund or not public fund the technology. This recommendation gets sent to the Ministry of Health and they decide whether to uphold the decision. Even if the committee makes a recommendation for public funding, it does not guarantee the Ministry will fund the technology.

For this HTA we are looking at noninvasive vagus nerve stimulators, these are small devices that are held against the skin of the neck to stimulate the vagus nerve to treat, prevent and reduce the severity of migraines/cluster headaches.

End of Interview: Next Steps

In terms of next steps, we are planning to present to the committee in April. Once the committee makes a decision, we go through an internal review process. After that, we post the decision for public comment. That's the next time you'll hear back from me. I'll email you with the decision and the link where you can comment on the committee's decision.

Interview Questions

Impact of Living With Migraine/Cluster Headache

- Can you describe your experience living with migraine/cluster headache?
  - Describe the symptoms of your migraine/cluster headache?
  - How long have you been experiencing these symptoms?
  - Suicide headache?
- What is the impact of migraine/cluster headache on your quality of life?

  Probe: Social life, mental health, work, family/care partners, day to day life

Care Journey

- Can you describe your diagnosis journey?
- Can you describe your treatment journey? Wait times to see specialists?
    - What treatment options have you explored? (i.e. medications)
        - What treatments have you tried to lessen the frequency, duration of your symptoms?
        - What treatments have you tried for prevention?
        - Preventative side effects?
        - Rural CH patients: limited access to inhaled oxygen and possible increased usage of verapamil + EKG monitoring?
    - Were the treatments effective in preventing/alleviating your symptoms?
    - Did you experience any side effects from your treatment?
    - Are you aware of/tried noninvasive vagus nerve stimulation devices that are applied at the neck?

  If yes:

    - How did you become aware of this treatment option?
    - How was your experience with the device?
        - How long have you tried out the device for?
    - Did you notice any positive/negative change with your symptoms while using the device?
        - Impact on prevention of headache vs frequency, duration of your symptoms
    - Change in use of other treatment options (reduction in medication)
    - Was the device easy/difficult to use?
    - How did you finance the device? (out-of-pocket or insurance)
        - On-going costs

  If no:

    - Would you be willing to try out this device? (if it is available, if it's covered vs. if you are paying out-of-pocket)
    - How do you feel about non-pharmacological treatment options such as this device for the treatment of migraine/CH?

Barriers

- Was there any barrier to you accessing noninvasive vagus nerve stimulation devices?
- Was there any out-of-pocket cost for your treatment?
- Are there any other barriers that you would like to note?

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We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

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