Anthem

Clinical UM Guideline

Subject: Vagus Nerve Stimulation
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Description

This document addresses the indications for use of an implantable vagus nerve stimulation (VNS) device, the electronic analysis of the implanted neurostimulator pulse generator system, and non-implantable (transcutaneous) VNS devices. These devices are used as a treatment of medically and surgically refractory seizures associated with intractable epilepsy. Implantable devices may deliver stimulation in an open-loop fashion with continuous but intermittent ('ON' and 'OFF' cycles) stimulation of the vagus nerve (a hand-held magnet allows on-demand stimulation to interrupt seizure activity), or may utilize detection of extra-cerebral indicators, for example, cardiac-based seizure detection (also known as "responsive devices", "devices with an automatic stimulation mode", or "closed loop devices") that specifically use tachycardia as a surrogate marker for seizure prediction.

Note: The use of vagal nerve *blocking* for the treatment of morbid obesity is addressed in the following document:

- CG-SURG-83 Bariatric Surgery and Other Treatments for Clinically Severe Obesity

Note: Please see the following related documents for other treatments of epilepsy:

- CG-MED-05 Ketogenic Diet for Treatment of Intractable Seizures
- CG-SURG-91 Minimally Invasive Ablative Procedures for Epilepsy
- MED.00057 MRI Guided High Intensity Focused Ultrasound Ablation for Non-Oncologic Indications
- SURG.00026 Deep Brain, Cortical, and Cerebellar Stimulation

Clinical Indications

Medically Necessary:

A. Implantation of a vagus nerve stimulation device is considered **medically necessary** in an individual with medically and surgically refractory seizures as evidenced by:
   1. Failure of more than one trial of single or combination antiepileptic medications, as evidenced by persistent seizures or intolerable side effects of drug therapy; and
   2. Individual has failed or is not a candidate for resective epilepsy surgery.

B. Electronic analysis of an implanted neurostimulator pulse generator system for vagus nerve stimulation is considered **medically necessary** when the implantation occurred because the above criteria were met.

C. Replacement or revision of an implanted neurostimulator pulse generator system (with or without lead changes) for vagus nerve stimulation is considered **medically necessary** when:
   1. The implantation occurred because the above criteria were met; **and**
   2. The current implanted device is no longer functioning appropriately.

Not Medically Necessary:

A. Implantation of a vagus nerve stimulation device is considered **not medically necessary** when criteria are not met and for all other conditions.

B. Electronic analysis of an implanted neurostimulator pulse generator system for vagus nerve stimulation is considered **not medically necessary** when the medically necessary criteria for device implantation are not met.

C. Replacement or revision of an implanted neurostimulator pulse generator system for vagus nerve stimulation (with or without lead changes) is considered **not medically necessary** when the medically necessary criteria for device implantation are not met or the current implanted device is functioning appropriately.

D. Non-implantable vagus nerve stimulation devices are considered **not medically necessary** for all conditions.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when specified as vagus nerve stimulator and criteria are met:

CPT	
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Open implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

95977	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

HCPCS

C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension

ICD-10 Procedure

00HE0MZ	Insertion of neurostimulator lead into cranial nerve, open approach
00HE3MZ	Insertion of neurostimulator lead into cranial nerve, percutaneous approach
00HE4MZ	Insertion of neurostimulator lead into cranial nerve, percutaneous endoscopic approach

ICD-10 Diagnosis

G40.001-G40.919	Epilepsy and recurrent seizures

When services are Not Medically Necessary:
For the procedure codes listed above when specified as vagus nerve stimulator when criteria are not met or for all other diagnoses not listed.

When services are also Not Medically Necessary:

HCPCS

E0735	Non-invasive vagus nerve stimulator
E1399	Durable medical equipment, miscellaneous [when specified as a transcutaneous (non-implantable) VNS device]

ICD-10 Diagnosis

	All diagnoses

Discussion/General Information

Medically and Surgically Refractory Seizures and VNS therapy

Pharmacotherapy is considered the first-line therapy in the treatment of seizures. Pharmacotherapy can result in seizure remission, reduced morbidity and decreased risk of premature mortality associated with sudden unexpected death in epilepsy (SUDEP) and other seizure-related complications related to seizures. Drug therapy is effective in approximately 66% of individuals with epilepsy. Surgery, consisting of a removal or disconnection of brain regions is the only epilepsy treatment considered curative. However, a significant number of individuals are not surgical candidates (Thijs, 2019). Greater than 50% of individuals with epilepsy are reported to have additional medical conditions some of which may preclude the individual from surgical treatment (Sinha, 2022).

Neurosurgery is associated with surgical risks such as hemorrhage and infection. Post-surgical deficits, including but not limited to memory, vision, mood and language may be temporary or permanent (Sinha, 2022). VNS surgery is considered a low surgical risk procedure in which complications are generally limited to superficial infection (3%-6%). Other risks, such as vocal cord paralysis and bradycardia/asystole are reported as rare (Simpson, 2022).

Surgery has been significantly and consistently underutilized by individuals with medication refractory seizures. Approximately 3000-4000 surgeries are done each year on an estimated 100,000-200,000 surgical candidates (Samanta, 2021). The surgical rate has remained static or decreased, despite high-level evidence and clinical practice guidelines supporting the efficacy of surgery (Englot, 2012; Samanta, 2021). This underutilization is attributed to multiple factors present in both affected individuals, their families, treating or referring physicians and healthcare systems (Dewar, 2021; Samanta, 2021). Sinha and associates (2021) published the results of a survey assessing individual acceptability of benefit-risk trade-offs when evaluating epilepsy treatment options. The authors noted:

> Many patients express the belief that brain surgery is a last resort and only for those with the most severe disease. Our results are generally in line with commonly held beliefs/-experience that many patients are willing to consider presurgical evaluation due to the availability of less invasive or lower risk options, such as LITT versus open brain surgery, but also neuromodulation versus surgical resection or ablation, and stereo electroencephalography (EEG) versus subdural electrodes for intracranial EEG evaluations.
>
> For many patients in this study, the lower potential benefit of a procedure is an acceptable trade-off to reduce the invasiveness and perhaps inconvenience of the procedure when offered as the initial surgical option. Interestingly, our results suggest that this may be independent of the potential for reduced risks of mortality and long-term neurological deficits.

Surgery is considered the most effective and long-lasting option for individuals with medically refractory seizures when the seizures emanate from a region that can be removed with minimal risk of disabling neurologic or cognitive dysfunction. However, for individuals who have been educated on the risks and benefits associated with surgery and who decline surgery, VNS therapy may be an acceptable option.

Implantable VNS

An implantable VNS device is similar to a cardiac pacemaker and includes a generator device surgically placed under the skin in the left chest area, typically below the collarbone. A nerve stimulation electrode is tunneled under the skin to the lower neck where it is placed around the left cervical vagus nerve. Using an external programmer, the stimulation parameters of the device are set (or reset) to deliver preprogrammed intermittent electrical pulses to the vagus nerve, which then transmits the stimulation to the brain to create widespread antiepileptic effects. Additionally, an individual can activate the system when sensing the onset of a seizure to deliver an additional dose of stimulation by passing a magnet over the area of the chest where the device is implanted. The device is powered

by a lithium thionyl chloride battery that must be replaced every 1.5-5 years depending on the stimulation parameters.

Reports of adverse effects of implantable VNS therapy have included voice alteration, headache, neck pain, cough, and obstructive or central sleep apnea (CSA)/sleep breathing disorders; however, “the mechanism for CSA seen in patients with a vagus nerve stimulator is not fully known” (Forde, 2017). In a review article, Giordano and colleagues (2017) report on surgical techniques for VNS implantation and related acute and delayed morbidity. Late complications of VNS therapy, related to the device and to stimulation of the vagus nerve include, but are not limited to delayed arrhythmias, laryngopharyngeal dysfunction (hoarseness, dyspnea, and coughing), obstructive sleep apnea, stimulation of the phrenic nerve, and tonsillar pain mimicking glossopharyngeal neuralgia. Complete surgical removal or revision and replacement of the device is considered in cases of device malfunction (4%-16.8%), failure of VNS therapy, intolerable side effects, or resulting from the individual’s specific request. Sleep breathing disorders and laryngeal motility alterations are reported in numerous single and small case series of individuals implanted with VNS for drug-resistant epilepsy. In a retrospective case series, Zambrelli and colleagues (2016) evaluated 23 individuals with medically refractory epilepsy who underwent sleep testing before and after VNS implantation. A total of 18 individuals underwent endoscopic laryngeal examination post-VNS implantation. Statistical analysis was carried out to assess an association between laryngeal motility alterations and the onset/worsening of sleep breathing disorders. After VNS implantation, 11 individuals showed new-onset of mild/moderate sleep breathing disorders. Individuals already affected by obstructive sleep apnea showed worsening of sleep breathing disorders, and those with new-onset obstructive sleep apnea had a laryngeal pattern with left vocal cord adduction (LVCA) during VNS stimulation. The authors suggest there is an association between VNS and sleep breathing disorders that should be investigated in individuals before and after VNS implantation.

Treatment of Medically and Surgically Refractory Seizures

In 1997, the U.S. Food and Drug Administration (FDA) approved a VNS device called the NeuroCybernetic Prosthesis (NCP®) system (Cyberonics, Inc. [now LivaNova USA, Inc., Houston, TX) through the premarket approval (PMA) process. The device was approved for use in conjunction with drugs or surgery “…as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures.” The company markets the system as VNS Therapy®.

The long-term efficacy and safety of VNS therapy in children with medically refractory seizures, including those with Lennox-Gastaut Syndrome (LGS), has been reported in numerous retrospective case series, multicenter and observational studies, and randomized controlled trials (RCTs) (Alexopoulos, 2006; Benifla, 2006; De Herdt, 2007; Elliott, 2011c; Healy, 2013; Klinkenberg, 2012; Kostov, 2009; Orosz, 2014; Tecoma, 2006; You, 2007; You, 2008). Additional retrospective case series measuring the long-term effects of VNS for medically and surgically refractory seizures in adults and the pediatric population have been published in the peer-reviewed medical literature. Significant reductions in seizure frequency with possible cumulative effect are reported along with a reduction in surgical complications and untoward side effects with chronic VNS therapy (Coykendall, 2010; Elliott, 2011a; Elliott, 2011b; Ghaemi, 2010; Kabir, 2009; Morris, 1999; Murphy, 1999; Siddiqui, 2010; Vale, 2011; Yu, 2014). Englot and colleagues (2011) performed the first meta-analysis of VNS efficacy in epilepsy, identifying 74 clinical studies with 3321 participants with intractable epilepsy. These studies included three blinded RCTs (Class I evidence); two nonblinded RCTs (Class II evidence); ten prospective studies (Class III evidence); and numerous retrospective studies. After VNS implantation, seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures at 3-12 months after surgery and a 51% reduction after greater than 1 year of therapy. At the last follow-up, seizures were reduced by 50% or more in approximately 50% of the individuals, and VNS therapy reported a ≥ 50% reduction in seizures (main effects, odds ratio of 1.83; 95% confidence interval [CI], 1.80-1.86). Individuals with generalized epilepsy and children benefited significantly from VNS despite their exclusion from initial approval of the device. Ryvlin and colleagues (2014) published a RCT reporting long-term quality of life outcomes for 112 individuals with drug-resistant focal seizures, which supports the beneficial effects of VNS for these groups.

In a Cochrane review, Panebianco and colleagues (2015) systematically reviewed the available evidence in the peer-reviewed medical literature for the efficacy and tolerability of VNS when used as an adjunctive treatment for individuals with drug-resistant partial epilepsy. In five trials which included 439 participants, VNS appeared to be effective and well tolerated for the treatment of partial seizures. Results showed a positive dose-response relationship regarding stimulation level and seizure frequency. An evaluation of outcomes related to "withdrawal of allocated treatment" suggested that VNS was well tolerated as withdrawals were rare. Adverse effects associated with implantation and stimulation included hoarseness, cough, dyspnea, pain, paresthesia, nausea and headache, with hoarseness and dyspnea more likely to occur on high stimulation than low stimulation.

In 2013, the American Academy of Neurology (AAN) (Morris) released an updated guideline evaluating the evidence regarding the efficacy and safety of VNS for epilepsy. This document was reaffirmed in 2022. The guideline states that VNS may be considered for seizures (both partial and generalized) in children, for LGS-associated seizures. VNS may also improve mood when used in the treatment of adults with epilepsy although this should be considered a secondary reason for VNS.

Harden and colleagues (2017) reported on the incidence rates and risk factors for SUDEP in different epilepsy populations in a 2017 practice guideline from the AAN and American Epilepsy Society. Considering a systematic review of the literature, the guideline states:

> The evidence is very low or conflicting that the following factors are associated with altering SUDEP risk:
>
> - Vagus nerve stimulator use for more than 2 years (however, current research does not rule out the possibility of a beneficial effect and, further, the potential effect of epilepsy surgery on reducing GTCS frequency and epilepsy severity on reducing the risk of SUDEP).

Closed Loop Systems

The automated stimulation function of a closed loop VNS model detects heart rate changes and automatically responds by sending a programmed stimulation to the vagus nerve. Cardiac signal changes may be used as a potential biomarker to indicate the ictal onset of epileptic seizures. Approximately 82% of individuals with epilepsy had at least one seizure associated with significant heart rate increases, which occur in the pre-ictal phase (Eggleston, 2014). The AspireSR or SenTiva devices were developed to take advantage of this extra-cerebral indicator of ictal onset and preemptively prevent seizures.

In 2015, the FDA approved the AspireSR generator, the first VNS Therapy System that provides responsive stimulation when tachycardia is detected. The AspireSR includes an autostimulation mode that utilizes a customizable cardiac algorithm to detect relative heart rate increases to predict ictal onset and deliver automatic vagus nerve stimulation to prevent seizures before they occur or more quickly end them when they do occur (closed loop system). The FDA approved the most recent implantable VNS therapy system, the SenTiva in October 2017. Like the AspireSR, the SenTiva device includes an autostimulation mode. The Sentiva also includes additional features such as small size, data gathering and a tablet-based interface. In addition to the autostimulation mode, both devices have a manual mode. Both devices are approved for use in individuals with drug-resistant epilepsy aged 4 years and older.

While RCTs directly comparing conventional (“open loop”) devices to devices with an automatic stimulation mode” (“closed loop”) have not been conducted, available evidence suggests that both devices are likely to produce at least equivalent therapeutic results (Boon, 2015; Hamilton, 2018; Tzadok, 2019). It is important to recognize that complete seizure freedom is rarely achieved using VNS therapy and that approximately 25% of individuals do not receive any benefit from therapy.

Treatment of Refractory Depression

In July 2005, Cyberonics, Inc. (now known as LivaNova USA, Inc, Houston, TX, USA) received FDA premarket approval for the VNS Therapy™ System “…for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.” The data presented to the FDA consisted of a case series of 60 individuals receiving VNS (Study D-01), a short-term (3-month) randomized sham-controlled clinical trial of 221 individuals (Study D-02), and an observational study comparing 205 individuals on VNS therapy to 124 individuals receiving ongoing treatment for depression (Study D-04) (George, 2005; Rush, 2000). Individuals who responded to sham treatment in the short-term RCT (approximately 10%) were excluded from the long-term observational study.

The primary efficacy outcome was the relief of depression symptoms, assessed by any one of many different depression symptom rating scales. A 50% reduction from baseline score was considered to be a reasonable measure of treatment response. In the studies evaluating VNS therapy, the four most common instruments used were the Hamilton Rating Scale for Depression (HAMD), Clinical Global Impression, Montgomery and Asberg Depression Rating Scale (MADRS), and the Inventory of Depressive Symptomatology Self-Related (IDS-SR). The case series data reported rates of improvement, as measured by a 50% improvement in depression score of 31% at 10 weeks to greater than 40% at 1 to 2 years. This appeared to stabilize out to 2 years, but there were substantial losses to follow-up (n=42 at 2 years versus original sample of 59) (Marangell, 2002; Rush, 2000; Sackeim, 2001). Natural history, placebo effects, and the expectations of the individual and their medical practitioner make it difficult to infer efficacy from this case series data.

The D-02 randomized trial (Rush, 2000; Rush, 2005a) compared VNS therapy to a sham control, (implanted but inactivated VNS), reporting a non-statistically significant result for the principal outcome at 3 months. A total of 15% of VNS participants responded versus 10% of control participants (p=0.31). The IDS-SR was considered a secondary outcome, showing a difference that was statistically significant in favor of VNS (17.4% versus 7.5%; p=0.04). All other outcomes assessed in the trial did not show statistically significant differences between groups.

The observational study comparing individuals participating in the RCT and a separately recruited control group (D-04 versus D-02) evaluated VNS therapy out to 1 year, showing a statistically significant difference in the rate of change of depression score (George, 2005; Rush, 2000). This study was conceived after the results of the RCT were known. The outcomes of this study, however, may have been confounded by issues such as unmeasured differences between individuals, nonconcurrent controls, differences in sites of care between individuals with VNS therapy and controls, and differences with regard to concomitant therapy changes. Analyses performed on subsets of individuals cared for in the same sites and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness of VNS with almost no statistically significant differences.

Aaronson and colleagues (2013) performed a multi-center double-blind study comparing the clinical outcomes of VNS therapy applied at different stimulation levels. VNS therapy was used as adjuvant treatment in 331 individuals with a history of chronic or recurrent bipolar disorder or a current episode of major depressive disorder. The intent of the trial was to show that “high” and “medium” electrical “doses” (charge) would produce superior clinical outcomes relative to a “low” electrical dose. Participants with a history of failure to respond to at least four adequate dose/duration antidepressant treatment trials from at least two different treatment categories were randomized to one of three dose groups. After 22 weeks, the current stimulation dose could be adjusted in any of the groups. At follow-up visits at weeks 10, 14, 18, and 22 after enrollment, there was no statistically significant difference between treatment groups in comparison of the primary outcome measure, a change in IDS-Clinician Administered (IDS-C) score from baseline. The mean IDS-C score improved significantly for each of the groups from baseline to 22-week follow-up. At 50 weeks of follow-up, the proportion of the small number of 22-week responders with a durable outcome was greater in the “high” and “medium” electrical “dose” groups than in the “low” dose group. Most participants completed the study; however, there was a high rate of reported adverse events, including voice alteration in 72.2%, dyspnea in 32.3%, and pain in 31.7%. Limitations of this study include the interpretation of improvement in IDS-C scores over time due to the lack of a controlled (no treatment) comparator group and, that approximately 20% of the participants had a history of bipolar disorder. Therefore, the results may not be representative of a homogeneous group of individuals with treatment-resistant unipolar depression.

Aaronson and colleagues (2017) evaluated long-term outcomes from the 5-year post-marketing surveillance study of individuals with TRD treated with VNS or “treatment as usual.” This multicenter, prospective, open-label, non-randomized, longitudinal, observational registry study conducted at 61 United States sites included 795 individuals who experienced a major depressive episode (unipolar or bipolar depression) of at least 2 years duration or had three or more depressive episodes (including the current episode), and who had failed four or more depression treatments (including ECT). Prior to enrollment, registry participants (except for those enrolled in the VNS dose-finding study, referred to as the D-21 study; NCT00305565) were allowed to select the treatment arm of their choice; however, some individuals were assigned by study site to receive the alternate treatment (n=301, number of participants in the treatment-as-usual arm). Participants in the VNS arm (n=494) underwent implantation surgery before visit 2 (baseline). Post-baseline follow-up visits for all participants were scheduled at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months. Data was collected on medical status, adjustment of mood disorder therapy, and concomitant treatments (with no restrictions). The primary efficacy measure was response rate, defined as a decrease of ≥ 50% in baseline MADRS score at any post-baseline visit during the 5-year study. Secondary efficacy measures included remission. Safety analysis included participants in the treatment-as-usual arm who completed the visit 2 requirements and those in the VNS arm who had undergone device implantation before visit 2. At baseline, the mean MADRS score was 29.3 (standard deviation [SD] equals 6.9) for the treatment-as-usual group and 33.1 (SD equals 7.0) for the VNS arm. The registry results indicated that participants in the VNS arm had better clinical outcomes than the treatment-as-usual group, including a significantly higher 5-year cumulative response rate (67.6% compared with 40.9%, respectively; p<0.001) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%, respectively; p<0.001). A subanalysis demonstrated that among participants who had previously responded to ECT, those in the VNS arm had a significantly higher 5-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%, respectively; p=0.006). For ECT nonresponders in the VNS arm, the response rate was 59.6% (95% CI, 50.2, 68.4), compared with 34.1% (95% CI, 21.8, 48.9) for ECT nonresponders in the treatment-as-usual arm (p<0.001), with statistically significant separation beginning after 2 years of treatment and continuing until completion of registry participation. Several limitations to this study exist, including those previously cited in the original study, and the long-term evaluation of data from a participant registry. The naturalistic, observational study design did not allow for random assignment of participants to treatment groups; thus, participants were not blinded to treatment. A significant number of participants in both groups withdrew early from the study. Of the 494 participants in the VNS arm, 461 (93%), 289 (59%), 313 (63%), 334 (68%), and 300 (61%), respectively, completed all 5 years of the registry (the variable numbers in the VNS arm are due to D-21 study participants who rolled over into the registry at various time points after implantation). Of the 301 participants in the treatment-as-usual arm, 224 (74%), 185 (62%), 168 (56%), 149 (50%), and 138 (46%), respectively, completed all 5 years of the registry. Of the 358 participants (45%) who withdrew early, 195 were from the VNS arm (40%) and 163 were from the treatment-as-

usual arm (54%). The reasons for early withdrawal were similar between the treatment arms. Finally, the significantly higher treatment response rate observed in the VNS arm may represent a treatment effect, as participants with an implanted device may have had a higher expectation of therapeutic improvement; in addition, inclusion of D-21 study rollover participants in the VNS arm who may have previously experienced a positive response with VNS may have been more likely to participate in the registry.

A 2022 clinical practice guideline on the management of major depressive disorder (Department of Veterans Affairs/Department of Defense) notes that although the FDA has approved VNS therapy as a treat of TRD, the guideline recommends against using VNS for this condition, citing evidence showing no difference between VNS and sham placebo. The guideline notes that the potential harms and burden outweigh the benefits and individuals "may try other non-pharmacological treatments for major depressive disorder over the use of VNS".

The American Psychological Association (APA) clinical practice guideline addressing the treatment of depressive disorders in children, adolescents, adults and older adults (2022) examined the efficacy of psychological treatments, pharmacotherapy and complementary and alternative medicine treatments. While there was a conditional recommendation for use for complementary and alternative treatments in adults, VNS was not listed as a specific modality in the recommended list.

Summary

While some studies results have suggested that VNS therapy may be effective at managing TRD, these studies have a number of limitations, namely a lack of a comparison group (Bajbouj, 2010; Cristancho, 2011; Nahas, 2005; Schlaepfer, 2008). Controlled studies have not provided clear evidence that VNS therapy is an effective non-pharmacological treatment of TRD (Aaronson, 2013; Rush, 2005). While there might be some evidence suggesting potential benefits, the therapy is yet to be recognized as a standard of care in medical practice in the treatment of TRD.

VNS Paired with Rehabilitation Following Stroke

In a pivotal, randomized, triple-blind, sham-controlled study VNS paired with rehabilitation was compared to the rehabilitation alone (Dawson, 2021). Participants met criteria if they had a history of unilateral supratentorial ischemic stroke that occurred 9 months to 10 years prior to enrollment, and a moderate to severe arm impairment defined as a Fugl-Meyer Assessment-Upper Extremity (FMA-UE) score of 20 to 50. The study involved 106 participants randomly assigned to receive either rehabilitation paired with active implanted VNS using the Vivistim® System (MicroTransponder, Austin, TX) or rehabilitation paired with implanted sham stimulation. Participants received 6 weeks of in-clinic therapy, 3 times per week for a total of 18 sessions followed by a home exercise program. The primary outcome was the change in impairment measured by an FMA-UE score measured on the first day after completion of in-clinic therapy. On the first day following completion of in-clinic therapy, the mean FMA-UE score increased by 5 points in the VNS group and 2.4 points in the control group (between group difference, 2.6; 95% CI, 1 to 4.2; p=0.0014). At 90 days after in-clinic therapy, a clinically meaningful response on the FMA-UE score was achieved in 23 (47%) of 53 participants in the VNS group compared to 13 (24%) of 55 participants in the control group (between group difference, 24%; p=0.0098). There was one serious adverse event related to surgery in the control group. It remains unclear if the outcomes of VNS paired with rehabilitation are maintained beyond 90 days.

Dawson and colleagues (2016) conducted a small, randomized pilot study of implantable VNS in individuals with upper limb dysfunction after ischemic stroke. A total of 21 individuals were randomized to VNS plus rehabilitation or rehabilitation alone. The mean change in the outcome as assessed by a functional assessment score was +8.7 in the VNS group versus +3.0 in the control group (p=0.064). Only 6 individuals in the VNS group achieved clinically meaningful response versus 4 individuals in the control group. Limitations of this study include the small sample size, lack of blinding to either the physiotherapist delivering the therapy or the subject, and no sham stimulation group.

The safety and feasibility of an implanted VNS as a potential therapeutic rehabilitative modality was investigated in a multisite, double-blinded, sham-controlled pilot study (Kimberley, 2018). Individuals with arm weakness following unilateral supratentorial ischemic stroke were randomized to receive rehabilitation with active VNS (n=8) or rehabilitation with control VNS (n=9). Participants received in-clinic therapy 3 times a week for 6 weeks followed by prescribed daily home exercises. Individuals in the control group were crossed over to active in-clinic treatment following the 90-day assessment. The FMA-UE tool was used to quantify improvement, with a clinically meaningful improvement defined as a 6 or more-point improvement over baseline. Following in-clinic therapy, there was no significant differences between the groups. At 90 days, the mean FMA-UE scores improved by 9.5 points in the active VNS group and 3.8 points in the control VNS group. The difference was attributed to maintained benefit in the active VNS group and a decline in the control VNS group and a higher percentage of participants who achieved a clinically meaningful response in the active VNS group. Individuals who crossed over to active treatment achieved results similar to the active VNS group. While the results of this pilot study with limited participants are promising, there were some limitations. At baseline, the mean FMA-UE was 29.5 with a SD of 6.4 in the active VNS group and 36 with a SD of 9.4 in the control VNS group. While compliance with home therapy was measured by downloading device information and self-report, compliance outcomes were not reported within the study.

Dawson and colleagues (2020) reported on the 1-year outcomes of the individuals from Kimberley (2018) pilot study. Outcomes were available for 15 of the 17 original participants. Adherence data was gathered using the number of magnetic swipes performed and correlating that to potential number of home exercise sessions performed. On average, participants performed home exercise 57.4% of the time (200±63 sessions). At 1 year, the pooled FMA-UE scores improved 9.2 ± 8.2 points (CI = 4.7 to 13.7, p = 0.001) over baseline. A clinically meaningful response at one year was reported by 73% (11/15) of participants. This study reported long-term gains associated with active VNS and a home exercise therapy. With the cross-over of the control group to active VNS treatment, the comparator exercise only group data was lost. While these results are promising, post-stroke deficits affect a significant number of individuals, this study included only 17 participants.

Summary

The use of VNS therapy as an adjunctive therapy during stroke rehabilitation has shown some potential benefits. The goal of rehabilitation following a stroke is to regain the ability to perform everyday activities and maximize function. Rehabilitation may include exercises, stretching, and training on assistive devices (Shahid, 2023). The use of VNS paired therapy is not considered a part of the standard of care in this population.

Use of VNS to treat conditions other than seizures:

Numerous small case series and retrospective studies of short duration have investigated implantable VNS therapy as treatment for essential tremor (Handforth, 2003), enhancing cognitive deficits in Alzheimer's disease (Merrill, 2006), anxiety disorders (George, 2008), and bulimia. Other review articles and studies explore the potential use of VNS in the treatment of acute asthma exacerbation (Miner, 2012; Yuan, 2015), autism (Danielsson, 2008), addictions, coma, intractable hiccups (Payne, 2005; Tariq, 2021), pain syndromes (such as fibromyalgia) (Lange, 2011), obesity-related food cravings in individuals with chronic TRD (Bodenlos, 2007), sleep disorders (such as narcolepsy), memory and learning deficits (Ansari, 2007), severe refractory cluster or migraine headaches

(Cecchini, 2009; Mauskop, 2005) or chronic heart failure (De Ferrari, 2011; Gold, 2016; Hauptman, 2012; Nearing, 2021; Premchand, 2014; Zannad, 2014). To date, the FDA has not cleared the use of any type of implantable VNS device for these indications. VNS has been evaluated to treat a number of medical conditions beyond medically refractory seizures; however, such use is not considered in accordance with generally accepted standards of medical practice.

Non-Implantable Transcutaneous VNS (t-VNS or n-VNS)

Cluster Headaches or Migraines

A non-implantable VNS device (also referred to as transcutaneous VNS [t-VNS] or n-VNS) requires no surgical procedure. Auricular t-VNS devices combine a stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve via skin over the concha of the ear. Another t-VNS device stimulates the cervical branch of the vagus nerve with a handheld device. Device users self-administer electric stimulation using prespecified device parameters agreed upon by the prescribing physician. Side effects of t-VNS are similar to those reported with an implantable VNS device, in addition to local skin irritation at the site of application.

On May 30, 2017, the FDA cleared the gammaCore-S® non-implantable VNS device (ElectroCore® Medical, LLC, Basking Ridge, NJ) for the treatment of acute pain associated with cluster headache in adults. On November 27, 2018, the FDA expanded clearance to include adjunctive use for the preventive treatment of cluster headaches in adults. In addition to the FDA indications for cluster headaches, the gammaCore device is FDA approved for the prevention and acute treatment of migraine headaches in both adolescents (age 12 and older) and adults.

Nesbitt and colleagues (2015) conducted an observational study of the gammaCore t-VNS device for the treatment of cluster headaches. A total of 25 individuals were prescribed t-VNS treatment over 12 months with instructions to record their change in condition. A total of 6 individuals were excluded, leaving 19 individuals (11 with chronic cluster headache and 8 with episodic cluster headache) in the final analysis. Individuals were administered up to 3 consecutive doses to treat an acute attack. For preventive use, they used 2-3 consecutive doses in the morning and late afternoon. A total of 15/19 individuals reported overall improvement with a mean overall self-estimated improvement of 48%. Prophylactic use significantly reduced the estimated mean attack frequency from 4.5/24 hours to 2.6/24 hours. The researchers concluded that the study “provides Class IV evidence that for patients with cluster headache, transcutaneous stimulation of the vagus nerve aborts acute attacks and reduces the frequency of attacks.”

Silberstein and colleagues (2016a) conducted a randomized, double-blind, sham-controlled prospective study (ACT1) evaluating t-VNS as acute treatment of cluster headache. Study participants were aged 18 to 75 years and were diagnosed with episodic cluster headache or chronic cluster headache according to the International Classification of Headache Disorders (ICHD)/International Headache Society (IHS) (2nd edition) criteria for ≥ 1 year before enrollment. A total of 150 participants were randomized (1:1) to receive t-VNS or sham treatment for ≤ 1 month during a double-blind phase; study completers could enter a 3-month t-VNS open-label phase. The primary endpoint was response rate, defined as the proportion of participants who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first cluster headache attack without rescue medication use through 60 minutes. Secondary endpoints included the sustained response rate (15-60 minutes). A total of 133 participants were included in the intention-to-treat population: all participants, 60 t-VNS-treated and 73 sham-treated; episodic cluster headache cohort: 38 t-VNS-treated, 47 sham-treated; and chronic cluster headache cohort: 22 t-VNS-treated, 26 sham-treated. A response was achieved in 26.7% of t-VNS-treated participants and 15.1% of sham-treated participants (p=0.1). On subset analysis, response rates were significantly higher in the episodic cluster headache cohort treated with t-VNS than in the sham-treated cohort (t-VNS, 34.2%; sham, 10.6%), but not the chronic cluster headache cohort (t-VNS, 13.6%; sham, 23.1%). Sustained response rates were significantly higher with t-VNS for the episodic cluster headache cohort and total population. A total of 35 of 150 participants reported adverse device effects (t-VNS, 11; sham, 24) in the double-blind phase and 18 of 128 participants in the open-label phase. Adverse device effects included application site reactions (such as burning, tingling, soreness, stinging or skin irritation, redness, or erythema), lip or facial drooping, pulling, or twitching, and dysgeusia or metallic taste. No serious adverse device effects were reported. In summary, participants with episodic cluster headache experienced clinical benefits in the t-VNS group over sham treatment, including rapid (within 15 minutes) and sustained (through 60 minutes) pain relief; although, significant treatment effects were not observed in participants with chronic cluster headache. In the final analysis, the response rate was not significantly different in t-VNS-treated versus sham-treated participants for the total study population.

Goadsby and colleagues (2017) conducted a randomized, double-blind, sham-controlled prospective study (ACT2; NCT01958125) in four European countries at nine tertiary care sites, including academic medical centers and headache/pain/neurology clinics, comparing non-implantable t-VNS with a sham device for acute treatment of individuals with episodic cluster headache or chronic cluster headache. The trial consisted of a 1-week run-in period; a 2-week, randomized, double blind period during which participants were treated with either t-VNS or a sham device; and a 2-week, open label period where all participants received t-VNS therapy. In the run-in period, participants were allowed to maintain their standard of care regimens (that is, rescue treatments, medications, and/or inhaled oxygen). Participants collected data throughout the study using paper diaries to record all cluster headache attacks, including pain intensity at onset and at 15 and 30 minutes after initiation of stimulation, rescue treatment use, number of stimulations used, and adverse events. The primary efficacy endpoint was the proportion of all treated attacks that achieved pain-free status within 15 minutes after treatment initiation, without rescue treatment. A total of 48 t-VNS-treated (n=14 episodic cluster headache; n=34 chronic cluster headache) and 44 sham-treated (n=13 episodic cluster headache; n=31 chronic cluster headache) participants were included in the full data analysis set. For the primary endpoint, t-VNS (14%) and sham (12%) treatments were not significantly different in the total cohort. In subgroup analysis, a significantly higher proportion of participants in the episodic cluster headache subgroup achieved pain-free status following treatment of attacks with t-VNS (48%) compared with sham treatment (6%). There was no significant treatment difference for this endpoint in the chronic cluster headache subgroup (t-VNS, 5%; sham, 13%). A total of 20 t-VNS-treated participants (40%) and 14 sham-treated participants (27%) had ≥ one adverse effect during the double-blind period, and 23 participants (23%) had ≥ one adverse effect during the open-label period. Limitations of this study include the short duration which did not allow for evaluation of continued/change in response with long-term t-VNS therapy and unequal number of participants in the cluster headache subtype groups, with less than 30% of participants comprising the episodic cluster headache group. In addition, during the open-label period, participants could alter their cluster headache treatment regimens by adding prophylactic therapies, or changing doses of existing treatments, or both, thus confounding the results and making it impossible to distinguish whether changes in efficacy outcomes were attributable to t-VNS therapy or to other changes in treatment during this period.

Gaul and colleagues (2016) reported the results of a prospective, randomized, open-label study (PREVA) of the gammaCore t-VNS device in the prophylactic treatment of chronic cluster headache. Participants aged 18 to 70 years were diagnosed with chronic cluster headache according to the ICHD/IHS (3rd edition) criteria for ≥ 1 year before enrollment The study included a 2-week baseline phase during which all participants received only their individualized standard of care (SoC) plan; a 4-week randomized phase during which participants were randomly assigned 1:1 by standard block design to receive either SoC plus t-VNS (prophylactic t-VNS; n=48) or SoC alone (control; n=49); and an optional 4-week extension phase during which all participants received SoC plus t-VNS. The t-VNS prophylaxis treatment consisted of three doses of 2-minute stimulations, 5 minutes apart, administered twice daily for a total of six doses per day to the right side of the neck (right vagal nerve). The first prophylactic treatment was administered within 1 hour of

waking; the second was administered 7 to 10 hours after the first treatment. If the cluster headache attack was not aborted within 15 minutes after stimulation, participants were instructed to take abortive medications (for example, subcutaneous sumatriptan, inhaled oxygen and intranasal zolmitriptan). The primary endpoint was the reduction in the mean number of cluster headache attacks per week. Response rate, abortive medication use and safety/tolerability were also assessed. At 4 weeks, the t-VNS group had a significantly greater reduction in the number of headaches than the control group, resulting in a mean therapeutic gain of 3.9 fewer headaches per week. The response rate, defined as a 50% or more reduction in cluster headaches, was 40% in the t-VNS group versus 8.3% in the control group ($p<0.001$). A total of 7 participants withdrew from the study due to adverse events; two adverse events (depressed mood and cluster headache) occurred in more than 1 participant. During the 2 months of treatment, similar proportions of participants in the SoC plus t-VNS group (52%; 25 of 48) and control group (49%; 24 of 49) reported one or more adverse events; most adverse events were mild or moderate (93%; 108 of 116). Among participants assigned to SoC plus t-VNS, 38% (18 of 48) experienced adverse events during the randomized phase and 25% (12 of 48) experienced adverse events in the extension phase. Among participants assigned to control, 27% (13 of 49) experienced adverse events during the randomized phase and 24% (12 of 49) experienced adverse events in the extension phase. Overall, the most common adverse events in any treatment group were cluster headache attacks, headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain. Limitations of this study include the open-label design and lack of a sham placebo/control group which may have resulted in response to treatment in the placebo t-VNS group, the short duration of treatment, and use of participant-reported outcomes that have the potential to bias the results.

Gaul and colleagues (2017) conducted a post hoc analysis of the PREVA study using a modified intent-to-treat population, defined as participants who had available data for each study week. The number of participants in the modified intent-to-treat population varied among the endpoints (including time to and level of therapeutic response) due to dependence on the availability of measurable observations. Of the 92 participants who continued into the 4-week extension phase, 44 participants continued to receive t-VNS plus SoC and 48 participants switched from SoC alone to t-VNS plus SoC. The mean weekly attack frequency was significantly lower with t-VNS plus SoC than with SoC alone from week 2 of the randomized phase through week 3 of the extension phase ($p<0.02$). Attack frequencies in the t-VNS plus SoC group were significantly lower at all study time points than at baseline. Attack frequencies were relatively stable throughout the extension phase. The global mean attack frequency at the end of the randomized phase had decreased by 40% from baseline in the t-VNS plus SoC group and had increased by 1% with SoC alone, representing a 41% therapeutic benefit of t-VNS ($p<0.001$). At the end of the randomized phase, a significantly higher percentage of participants in the t-VNS plus SoC group than in the SoC group had ≥ 25%, ≥ 50%, and ≥ 75% attack frequency reductions from baseline. Three participants (8%) in the t-VNS plus SoC group had a 100% attack frequency reduction; no participants in the SoC group had a 100% response. Safety and tolerability were as previously reported in the PREVA study, with similar proportions of participants in the t-VNS plus SoC and SoC groups reporting greater than or equal to one adverse event. Rates of discontinuation due to adverse events were also similar between groups. However, limitations of the PREVA study remain and limit the quality of evidence provided by this analysis.

Marin and colleagues (2018) performed a multicenter, retrospective study of the gammaCore t-VNS device for individuals with cluster headaches. The researchers reviewed data from 30 participants (29 with chronic cluster headaches and 1 with episodic cluster headaches) who used t-VNS after an inadequate response and/or intolerable side effects with ≥ 3 current or previous treatments. The participants were instructed to use t-VNS for preventive therapy, acute therapy, or both. The mean duration of the evaluation period was 7.6 months (0.9-27.5). The mean range of attack frequency with SoC alone was 26.6 (3.8-77.0) attacks/week compared to 9.5 (0-38.5) with SoC plus t-VNS ($p<0.01$). A total of 3 participants, who averaged 42 to 63 attacks/week before t-VNS, had no attacks during the evaluation period (range from 1.7 to 13.2 months). For the 25 participants who reported duration of attacks, the mean decreased from 51.9 minutes with SoC alone to 29.4 minutes with SoC plus t-VNS ($p<0.01$). In the 18 participants who reported severity, the mean decreased from 7.8 with SoC alone to 6.0 with SoC plus t-VNS ($p<0.01$). No serious adverse events were reported. The study was limited by a retrospective design and small sample.

Several small studies have evaluated the gammaCore device for migraine treatment and prophylaxis (Goadsby, 2014; Kinfe, 2015 [n=20 participants]). Goadsby and colleagues (2014) performed an open-label pilot study of portable t-VNS for the treatment of acute migraine with or without aura. A total of 27 from an initial sample size of 30 participants self-treated 80 migraine attacks (2 participants treated no migraine attacks with the device; 1 participant treated only an aura). Of the 54 moderate or severe attacks treated, 12 participants (22%) were pain free at 2 hours post treatment. Adverse events reported by 13 participants were all considered mild or moderate.

In an open-label, single-arm, multicenter study, Barbanti and colleagues (2015) evaluated the effects of the gammaCore t-VNS device for high-frequency episodic migraine (HFEM) and chronic migraine (CM). A total of 50 individuals (HFEM n=14; CM n=36) were enrolled, and 131 attacks were analyzed. Exclusion criteria included those with a history of cerebrovascular, cardiovascular, atherosclerotic, or significant neurological disease. Also excluded were those with significant systemic disorders or implanted electrical devices. Individuals were instructed to use t-VNS to self-treat up to three migraine attacks that occurred over 2 weeks. For each migraine, individuals delivered two doses at 3 minutes intervals within 20 minutes of mild or moderate pain onset. Individuals were allowed to take rescue medication if they had no reduction in pain within 2 hours. They rated their pain using a visual analog scale (VAS) and recorded symptoms and adverse events. Pain relief was defined as a ≥ 50% reduction in VAS score, and pain-free was defined as a VAS score of 0. The primary endpoint was pain-free status at 2 hours. At the end of the evaluation period, 27/48 individuals (56.3%) reported pain relief at 1 hour, including 17 individuals (35.4%) who were pain free. At 2 hours, 31 individuals (64.6%) reported pain relief, including 19 (39.6%) who were pain free. When all attacks were combined (n=131), the pain-relief rate was 38.2% at 1 hour and 51.1% at 2 hours. For all combined attacks, the pain-free rate was 17.6% at 1 hour and 22.9% at 2 hours. Rescue medications were taken in 53.4% (70/131) of the attacks. The researchers noticed that t-VNS was more effective in those with HFEM than CM. No major adverse events were reported. The authors concluded that t-VNS was able to achieve pain relief without serious side effects. The study was limited by the open-label design, short duration, and lack of a control group.

Silberstein and colleagues (2016b) evaluated the feasibility, safety, and tolerability of t-VNS in a prospective, multicenter, double-blind, sham-controlled pilot study of t-VNS for the prevention of chronic migraine attacks in adults (EVENT study). A total of 59 participants (mean age, 39.2 years) with chronic migraine (15 headache days/month; mean headache frequency, 21.5 days/month) entered the baseline phase (1 month) and were subsequently randomized to t-VNS or sham treatment (2 months) before receiving open-label t-VNS treatment (6 months). The primary endpoints were safety and tolerability. Efficacy endpoints in the intent-to-treat population included change in the number of headache days per 28 days and acute medication use. During the randomized phase, tolerability was similar for t-VNS (n=30) and sham treatment (n=29). Most adverse events were mild or moderate and transient (upper respiratory tract infections and gastrointestinal symptoms). Mean changes in the number of headache days were -1.4 (t-VNS) and -0.2 (sham) ($p=0.56$). A total of 27 participants completed the open-label phase. For the 15 completers initially assigned to t-VNS, the mean change from baseline in headache days after 8 months of treatment was -7.9 (95% CI, -11.9 to -3.8; $p<0.01$). Limitations of this study include the small sample size and high discontinuation rate. The investigators noted that blinding to active or sham treatment was “challenging, especially in comparison with drug studies.” In addition, the missing data and high discontinuation rates occurring disproportionately across treatment groups could affect study outcomes.

The FDA approval of the gammaCore t-VNS device for migraines was based on the “Prospective Study of nVNS for the Acute

Treatment of Migraine (PRESTO)" randomized sham-controlled trial (Tassorelli, 2018). A total of 248 participants with episodic migraines (with or without aura) were randomized to receive t-VNS (n=120) or sham treatment (n=123) within 20 minutes of pain onset, with a repeat treatment available if the pain had not improved in 15 minutes. Inclusion criteria included participants 18-75 years old, a diagnosis of migraine based on ICHD-3 beta criteria, < 50 years old at migraine onset, and attack frequency of 3-8 attacks a month with < 15 headache days per month over the last 6 months. Participants on migraine medication were required to have a stable dose and frequency schedule 2 months before the study, and participants could not start new medications during the study. Device training was provided to the participants by an unblinded trainer; participants and investigators were blinded prior to and during the study for the primary endpoint. The primary endpoint was the proportion of participants who were pain-free up to 120 minutes after a first attack without using medication. Pain was defined according to the IHS guidelines. After the first treated migraine attack, the proportion of participants in the t-VNS group who were pain-free was significantly higher at 30 and 60 minutes but not at 120 minutes. However, a post-hoc repeated measures test found t-VNS to be superior to sham for the pain-free outcome through 30, 60, and 120 minutes (odds ratio [OR] 2.3; 95% CI, 1.2 to 4.4; p=0.012). The most common adverse events were application site discomfort and nasopharyngitis; no serious adverse events were reported. The researchers concluded that the study demonstrates "the efficacy of nVNS for aborting attacks as early as 30 minutes and up to 60 minutes and for relieving pain at 120 minutes in the acute treatment of episodic migraine with or without aura." These findings only represent the 8-week study period. Post-hoc analysis provided additional promising information and insights regarding the results of this study (Grazzi, 2018; Martelletti, 2018). However, the findings are still limited by the short-term study period.

Diener and associates (2019) evaluated the use of non-invasive vagus nerve stimulation (nVNS) in the prevention of episodic migraine. The PREMIUM trial is a phase 3, prospective, multicenter, double-blind, sham-controlled, randomized trial intended to evaluate efficacy, tolerability and safety using an intent-to-treat (ITT) population. Adults aged 18 to 75 with a history of migraines who experienced 5-12 migraine days per month in the past 4 months, with at least 2 migraines lasting more than 4 hours, were eligible to participate. Participants were randomized to receive the GammaCore VNS device (n=169) or a sham device (n=172). The sham device produced a low-frequency biphasic direct current signal, which was intended to be perceived by the user but did not stimulate the vagus nerve or contract the muscle. Preventive treatment involved administering 2 consecutive bilateral stimulations 3 times a day. The study began with a 4-week run-in period of no study treatment, a 12-week period of use of either the VNS or sham device, followed by a 24-week open label period of VNS. The primary endpoint was mean reduction in number of migraine days per month. The use of the VNS device was not shown to be superior to the use of the sham device. Following the blinded portion of the study, the ITT population reported migraine reductions of -2.26 days in the VNS device group and -1.80 days in the sham device group (p=0.15). The authors noted that treatment responses to the VNS device (migraine and headache days) were maintained during the open-label period. The study had several limitations, including suboptimal adherence to the treatment protocol in both groups, and a significant drop-out rate among participants. The authors noted that the sham device was not inert, providing some vagus nerve stimulation which might have decreased the therapeutic gain in the VNS device group. Finally, the daily treatment protocol required bilateral stimulations, which authors noted could have mitigated the overall efficacy of the device.

Natelson and colleagues (2021) published the results of a randomized controlled trial evaluating the effects of nVNS using the gammaCore device compared to sham stimulation on the relief of widespread pain and migraine in Gulf War Veterans with Gulf War Illness (GWI). Participants were randomized to receive 10-week blinded treatment with either nVNS or sham stimulation followed by a 10-week open-label follow-up with active nVNS. Among the 27 participants there was a slight improvement in pain ratings from baseline to the end of the blinded phase (6.18 compared to 5.05, p=0.040) with no difference between the active or sham nVNS groups. There were no significant changes in migraine frequency or severity during the blinded phase.

The American Headache Society (Ailani, 2021) published a consensus statement on the integration of new migraine treatments into clinical practice. The American Headache Society recommends the use of gepants, ditans, or neuromodulatory devices, including noninvasive vagus nerve stimulation, for the acute treatment of migraines for which there is a contraindication or intolerance to triptan medications, or in individuals with inadequate response to two or more oral triptans. The statement regarding noninvasive vagus nerve stimulation was based on a review of Tassorelli (2018). While neuromodulatory devices "can also be considered" according to the statement, the use of these devices in clinical practice has been limited.

Other Conditions

Other t-VNS devices have been developed to transcutaneously stimulate the vagus nerve for the treatment of conditions including epilepsy, depression, irritable bowel syndrome, migraine headache, impaired glucose tolerance, schizophrenia, and tinnitus. One device, the transcutaneous VNS System (t-VNS®) with *NEMOS®* (CerboMed GmbH, Erlangen, Germany) received European clearance (CE mark) in 2011 for treatment of drug-resistant epilepsy. This device uses a combined stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve, which supplies the skin over the concha of the ear. Device users self-administer electrical stimulation for several hours a day; no surgical procedure is required. The device received the CE mark in Europe in 2011 but has not received FDA 510(k) clearance for use in the United States. Other studied transcutaneously-applied auricular VNS devices include, but are not limited to, the TENS-200 and TENS-220 (Hua Tuo, Suzhou, China) and the Tinnoff Profiler (Tinnoff, Inc., Helsinki, Finland). To date, the FDA has not cleared or approved any non-implantable t-VNS device for use in the treatment of any conditions other than headaches or migraines.

Pharmacoresistant Epilepsy

The safety and effectiveness of non-implantable, t-VNS therapy has been investigated for the treatment of individuals with chronic, drug-resistant epilepsy. He and colleagues (2013) conducted a small pilot study of 14 children with intractable epilepsy using an auricular t-VNS device (TENS-200) for 24 weeks as an adjunct to their current medication regimen. The mean reduction in seizure frequency from baseline through week 8, weeks 9 through 16, and weeks 17 through 24 was 31.8%, 54.13%, and 54.2%, respectively. The investigators found no correlation between the therapeutic efficacy of t-VNS and baseline seizure frequency reduction. In addition, neither age, gender, nor seizure syndrome predicted response to the device. In terms of reported side effects, t-VNS was well tolerated and only 2 participants reported mild ulceration of the skin at the stimulation area. Limitations of this study include the small sample size and lack of a control group.

Stefan and colleagues (2012) evaluated t-VNS therapy (using an unspecified CerboMed device) in a small case series of 10 adults with drug-resistant epilepsy. Stimulation via the auricular branch of the vagus nerve of the left tragus was delivered 3 times per day for 9 months. Subjective documentation of stimulation effects was obtained from self-reported seizure diaries. An assessment of seizure frequency was evaluated with prolonged outpatient video electroencephalography (EEG) monitoring. Other evaluations included computerized testing of cognitive, affective, and emotional functions. Three participants withdrew from the study with 5 of the remaining 7 participants reporting an overall reduction of seizure frequency after 9 months of t-VNS. A major discrepancy was noted, however, between subjective reports of seizure activity and quantified video-EEG in 2 participants. One participant reported a 37% reduction of seizure frequency (baseline: 21 seizures per week; average of months 7 to 9: 13.3 seizures per week) but an increase in seizures was recorded during outpatient video-EEG monitoring. A second participant reported a significant increase in simple partial seizures with subjective signs (baseline: 1.6 seizures per week; average of months 7 to 9: 4.2 per week), but no changes were seen on EEG recording. Non-implantable t-VNS was well-tolerated with side effects limited to hoarseness, headache or obstipation.

Limitations of this study include the small sample size and lack of a randomized control group.

Aihua and colleagues (2014) reported results from a case series of 60 individuals with pharmacoresistant epilepsy treated with a t-VNS device (TENS-200). A total of 60 participants were equally randomized to receive either stimulation over the earlobe (control group) or the Ramsay-Hunt zone, which includes the external auditory canal and the conchal cavity and is considered to be the somatic sensory territory of the vagus nerve. Four participants from the treatment group and 9 participants from the control group were excluded from analysis due to loss to follow-up (n=3, treatment group; n=2, control group); adverse effects (n=1, treatment group), or increase or lack of decrease in seizures or other reasons (n=7, control group). Compared with baseline, the median monthly seizure frequency in the treatment group was significantly reduced after 6 months (5.5 versus 6.0; p<0.001) and 12 months (4.0 versus 6.0; p<0.001) of t-VNS therapy. However, the median seizure frequency in the treatment group was not significantly lower than that in the control group until 12 months of treatment (4.0 versus 8.0; p<0.001). Limitations of this study include the small sample size, potential for unblinding in the control group as participants brought the instruments home for daily use and may have realized that they were in sham stimulation, and the study focused on seizure frequency with no comparison of different seizure syndromes.

Shiozawa and colleagues (2015) published the results of a systematic review of the peer-reviewed medical literature through 2013 evaluating the clinical utility of t-VNS and trigeminal nerve stimulation. Three t-VNS clinical trials assessed physiological features (that is, brain activation patterns and pain thresholds) in healthy volunteers, and one trial evaluated use in individuals with pharmacoresistant epilepsy. One study was a crossover design and the remaining trials were open-label studies. This analysis was limited in drawing conclusions due to lack of standardization of study design and small study populations (n=84).

Bauer and colleagues (2016) performed a randomized, two-arm, parallel group, prospective, double-blind, controlled clinical trial (cMPsE02) at nine sites in Germany and one site in Austria to assess the efficacy and safety of t-VNS (using the *NEMOS* device) compared with control stimulation in individuals with drug-resistant epilepsy. Individuals were eligible for study participation if they had a history of greater than or equal to three focal and/or generalized seizures per month, not more than 21 consecutive seizure-free days, and on a stable regimen of less than or equal to three antiepileptic drugs for at least 5 weeks prior to study enrollment and maintained this drug regimen throughout the study. Following an 8-week baseline period during which seizure rate was self-documented in a diary, 76 participants were randomized in a 1:1 ratio to treatment with either active t-VNS (that is, 25 Hz stimulation frequency, 250 µs pulse width, 30 s on/30 s off) or low level (active control, 1 Hz stimulation frequency, 250 µs pulse width, 30 s on/30 s off) t-VNS for 4 hours daily for 20 weeks. Two baseline visits (weeks 0 and 4) and 7 treatment visits (weeks 8, 9, 12, 16, 20, 24, 28) were performed. The primary objective was to demonstrate superiority of add-on therapy with t-VNS (stimulation frequency 25 Hz, n=39) versus active control (1 Hz, n=37) in reducing seizure frequency over 20 weeks. The investigators reported that treatment adherence was 84% in the 1 Hz group and 88% in the 25 Hz group, respectively. A total of 58 participants (76%) completed the study; 8 participants in the 1 Hz group and 10 participants in the 25 Hz group prematurely discontinued the study. The mean seizure reduction per 28 days at end of treatment as compared to baseline was -2.9% in the 1 Hz group and 23.4% in the 25 Hz group (p=0.146). For those individuals in the 25 Hz group who completed the full treatment period, a significant reduction in seizure frequency occurred in comparison to the control group (20 weeks; n=26, 34.2%; p=0.034). Responder rates (25%, 50%) were similar in both groups. On subgroup analyses, no significant differences were reported for seizure type and baseline seizure frequency. Any self-reported adverse events were mild or moderate and consisted of headache, ear pain, application site erythema, vertigo, fatigue, and nausea. Four serious adverse events were reported, including one sudden unexplained death in the 1 Hz group which was assessed as not treatment related. According to the investigators, the most relevant limitation of this study is that stimulation intensity was significantly higher in the 1 Hz group as compared to the 25 Hz group, “which may have reduced the difference in treatment efficacy between both groups.” Approximately one-third of study participants were not on any anticonvulsant medication, which is an unusually high rate and may limit generalizability of the results. Finally, the collection of data in self-maintained participant diaries may limit the accuracy of seizure quantification by some participants.

Summary

In addition to pharmacoresistant epilepsy, t-VNS therapy has been evaluated for a number of conditions including schizophrenia, tinnitus, impaired glucose tolerance and heart failure (Hasan, 2015; Huang, 2014; Kreuzer, 2014; Lehtimaki, 2014; Li, 2022; Stavrakis, 2020). The results of these limited studies have not the impacted standard of care for these conditions, which does not currently include t-VNS as an appropriate therapy for any of these conditions.

Definitions

Focal seizure: A seizure that begins with an electrical discharge in a relatively small area (called the focus) of the brain; previously referred to as a partial or localization-related seizure. In most cases, the cause is unknown, but may be related to a brain infection, head injury, stroke, or a brain tumor.

International Classification of Headache Disorders (ICHD): Classification and diagnostic criteria of headache disorders published by the International Headache Society (IHS) and incorporated into the 10th edition of the International Classification of Diseases (ICD-10).

Medically refractory seizures: Seizures that occur despite treatment with therapeutic levels of antiepileptic drugs or seizures that cannot be treated with therapeutic levels of antiepileptic drugs because of intolerable adverse side effects.

Migraine headache: A vascular headache believed to be caused by blood flow changes and certain chemical changes in the brain leading to a cascade of events that include constriction of arteries supplying blood to the brain that result in severe head pain, stomach upset, and visual disturbances.

Refractory depression: A major depressive disorder that fails to demonstrate an adequate response to an adequate treatment trial of antidepressant medications (for example, sufficient intensity of treatment for sufficient duration); also referred to as treatment-resistant depression (TRD). Potential factors contributing to apparent non-response include trial adequacy, individual compliance, differential diagnosis, and treatable comorbid conditions.

Vagus nerve: A nerve that controls both motor and sensory functions of the gastrointestinal tract, heart and larynx; also referred to as the 10th cranial nerve.

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    - Epilepsy.
    - Lennox-Gastaut Syndrome.

Index

AspireSR Model 106
CardioFit
gammaCore
gammaCore-S
Sentiva Model 100
t-VNS System with *NEMOS*
Vivistim
VNS Therapy

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
New	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Moved content of SURG.00007 to clinical utilization management guideline document with the same title.

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guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.