Vagus and External Trigeminal Nerve Stimulation (for Louisiana Only)

Policy Number: CS129LA.~~I~~M
Effective Date: ~~January 1, 2022~~TBD

➲ Instructions for Use

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Application

This Medical Policy only applies to the state of Louisiana.

Coverage Rationale

~~**Implantable vagus nerve stimulators are proven and medically necessary for treating epilepsy in individuals with all of the following** (see below for **unproven and not medically necessary** implants that allow detection and stimulation of increased heart rate):~~

- ~~Medically refractory epileptic seizures with failure of two or more trials of single or combination antiepileptic drug therapy or intolerable side effects of antiepileptic drug therapy; and~~
- ~~The individual is not a candidate for epilepsy surgery, has failed epilepsy surgery, or refuses epilepsy surgery after Shared Decision Making discussion; and~~
- ~~No history of left or bilateral cervical vagotomy. The U.S. Food and Drug Administration (FDA) identifies a history of left or bilateral cervical vagotomy as a contraindication to vagus nerve stimulation.~~

Vagus Nerve Stimulators

State Specific Criteria

Consideration shall be given for Medicaid reimbursement for implantation of the vagus nerve stimulator (VNS) if the treatment is considered medically necessary, the recipient

meets the published criteria, and the recipient has a diagnosis of medically intractable epilepsy.

The following criteria are used to determine recipient eligibility and approval of the VNS:
•Partial epilepsy confirmed and classified according to the International League Against Epilepsy (ILAE) classification. The recipient may also have associated generalized seizures, such as tonic, tonic-clonic, or atonic. The VNS may have efficacy in primary generalized epilepsy as well.
•Age 12 years or older, although case by case consideration may be given to younger children who meet all other criteria and have sufficient body mass to support the implanted system.
•Seizures refractory to medical anti-epilepsy treatment, with adequately documented trials of appropriate standard and newer anti-epilepsy drugs or documentation of recipient's inability to tolerate these medications.
•Recipient has undergone surgical evaluation and is considered not to be an optimal candidate for epilepsy surgery.
•Recipient is experiencing at least four to six identifiable partial onset seizures each month. Recipient must have had a diagnosis of intractable epilepsy for at least two years. The two-year period may be waived if waiting would be seriously harmful to the recipient.
•Recipient must have undergone quality of life (QOL) measurements. The choice of instruments used for the QOL measurements must assess quantifiable measures of daily life in addition to the occurrence of seizures.
•In the expert opinion of the treating physician, there must be reason to believe that QOL will improve as a result of implantation of the VNS. This improvement should occur in addition to the benefit of seizure frequency reduction. The treating physician must document this opinion clearly in the request for prior authorization (PA).

Exclusion Criteria

Regardless of the criteria for recipient selection, authorization for VNS implantation shall not be given if the recipient has one or more of the following criteria:
•Psychogenic seizures or other non-epileptic seizures,
•Insufficient body mass to support the implanted system,
•Systemic or localized infections that could infect the implanted system, or
•A progressive disorder contraindicated to VNS implantation, e.g., malignant brain neoplasm, Rasmussen's encephalitis, Landau-Kleffner syndrome and progressive metabolic and degenerative disorders.

Non-State Specific Criteria

Implantable vagus nerve stimulators are unproven and not medically necessary for treating all other conditions due to insufficient evidence of efficacy. These conditions include but are not limited to:

- Alzheimer's disease
- Anxiety disorder
- Autism spectrum disorder
- **Autoimmune disorders**
- Back and neck pain
- Bipolar disorder
- Bulimia
- Cerebral palsy
- Chronic pain syndrome
- Cluster headaches
- Depression
- Fibromyalgia
- Heart failure
- Migraines
- Morbid obesity
- **Musculoskeletal disorders**
- Narcolepsy
- Obsessive-compulsive disorder
- Paralysis agitans
- Sleep disorders

- Tourette's syndrome
- **Upper limb impairment related to stroke**

The following devices are unproven and not medically necessary due to insufficient evidence of efficacy:

- **Responsive vagus nerve stimulation implants (closed loop technology) that allow detection and stimulation based upon increased heart rate (e.g., AspireSR™ Model 106, SenTiva™ Model 1000) for treating epilepsy**
- Transcutaneous (non-implantable) vagus nerve stimulation (e.g., gammaCore® for headaches) for preventing or treating all indications
- Vagus nerve stimulation implants that allow detection and stimulation of increased heart rate (e.g., AspireSR™ Model 106, SenTiva™ Model 1000) for treating epilepsy

Trigeminal Nerve Stimulators

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- ~~Transcutaneous (non-implantable) vagus nerve stimulation (e.g., gammaCore® for headaches) for preventing or treating all indications~~
- External or transcutaneous (non-implantable) trigeminal nerve stimulation devices (e.g., Monarch® eTNS System, Cefaly®) for preventing or treating **all** conditions including but not limited to:
  - Attention deficit hyperactivity disorder (ADHD)
  - Depression
  - Epilepsy
  - Headache

~~Definitions~~

~~**Shared Decision Making:** Shared Decision Making is a process in which a provider and a patient (including caregivers and family) work together to make a health care decision about what is best for the patient. The optimal decision considers evidence based information about available options, the provider's experience and knowledge, and the values and preferences of the patient. This includes comparing the benefits, harms, and risks of each option and discussing what matters most to the patient (AHRQ, The SHARE Approach. Putting Shared Decision Making into Practice: A User's Guide for Clinical Teams, 2014).~~

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	**Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays**
*64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Open implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator

CPT® is a registered trademark of the American Medical Association

HCPCS Code	Description
E0770	Functional electrical stimulator, transcutaneous stimulation of nerve and/or muscle groups, any type, complete system, not otherwise specified
E1399	Durable medical equipment, miscellaneous
***K1016**	**Transcutaneous electrical nerve stimulator for electrical stimulation of the trigeminal nerve**
***K1017**	**Monthly supplies for use of device coded at K1016**
***K1020**	**Noninvasive vagus nerve stimulator**
*L8679	Implantable neurostimulator, pulse generator, any type
*L8680	Implantable neurostimulator electrode, each
*L8682	Implantable neurostimulator radiofrequency receiver
*L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
*L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
*L8686	Implantable neurostimulator pulse generator, single array, ~~nonrechargeable~~ **non-rechargeable**, includes extension
*L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
*L8688	Implantable neurostimulator pulse generator, dual array, ~~nonrechargeable~~ **non-rechargeable**, includes extension

Codes labeled with an asterisk (*) are not on the Louisiana Medicaid Fee Schedule and therefore may not be covered by the state of Louisiana Medicaid Program.

Description of Services

Vagus nerve stimulation(VNS) is a treatment for epilepsy where electrical impulses are delivered to the brain via the vagus nerve. This involves the implantation of a generator device to send electrical impulses to the cervical portion of the vagus nerve via stimulating leads surgically placed around the vagus nerve in the carotid sheath. The vagus nerve in turn sends signals to the brain which stimulate the area of the brain

believed to be involved in seizure activity. The mechanism of effect of VNS is currently unclear, but several pathways have been proposed and studied so far, including an increase in the release of neurotransmitters, such as norepinephrine and serotonin, increased cerebral blood flow to the thalamus and cortex and desynchronization of the alpha rhythms, as observed on EEG (Tzadok et al. 2019). There are two types of vagus nerve stimulators, the first being the conventional or open-loop that provides two modes of stimulation: normal mode (the device stimulates according to preset parameters) and/or magnet mode (gives a single, on-demand stimulation).The second is the newer responsive VNS model that uses closed-loop technology. This device has an auto stimulation function that detects heart rate changes and automatically sends a stimulation to the vagus nerve. Selection criteria and predictors of benefit are still being studied for this technology.

Non-implantable VNS devices (also referred to as n-VNS or transcutaneous VNS [t-VNS]) are being investigated as a noninvasive alternative to implantable VNS for indications such as pain, epilepsy, tinnitus, and depression. An example of this type of device is gammaCore (ElectroCore, LLC) which is a noninvasive handheld prescription device intended to deliver transcutaneous vagus nerve stimulation for the acute treatment of pain associated with episodic cluster headache

~~The vagus nerve, a large nerve in the neck, connects the lower part of the brain to the heart, lungs and intestines. Vagus nerve stimulation (VNS) uses short bursts of electrical energy directed into the brain via the vagus nerve. Implantable vagus nerve stimulators are implanted subcutaneously in the upper chest. These systems include a pulse generator/neurostimulator and electrode that deliver pulses of current to the left vagus nerve. Following implantation, the generator is programmed to stimulate the vagus nerve at a rate determined by the individual and physician. These devices generally have two types (modes) of stimulation: normal (the device stimulates according to preset parameters) and magnet (gives a single, on-demand stimulation). It is an expectation that the physician have experience and expertise in the use of vagus nerve stimulation.~~

~~The AspireSR Model 106 (Cyberonics now known as LivaNova) is an implantable vagus nerve stimulation generator that has an additional, optional mode called AutoStim Mode or Automatic Stimulation. This mode monitors and detects tachycardia heart rates, which may be associated with an impending seizure, and automatically delivers stimulation to the vagus nerve. The effect of the AutoStim Mode on reducing the number of seizures is being evaluated.~~

~~The Sentiva Model 1000 (LivaNova) is an implantable vagus nerve stimulation generator. It is a closed loop system that detects and responds to heart rate increases typical of many seizure types (Auto-Stim). Refer to the following website for more information: https://www.epilepsy.com/article/2017/10/new-vns-therapy-device-receives-fda-approval. (Accessed November 17, 2020)~~

~~Non-implantable VNS devices (also referred to as n-VNS or transcutaneous VNS [t-VNS]) are being investigated as a noninvasive alternative to implantable VNS for indications such as pain, epilepsy, tinnitus, and depression. An example of this type of device is gammaCore (ElectroCore, LLC) which is a noninvasive handheld prescription device intended to deliver transcutaneous vagus nerve stimulation for the acute treatment of pain associated with episodic cluster headache.~~

External or transcutaneous trigeminal nerve stimulation (TNS) is a non-invasive therapy that delivers signals to the brain via the trigeminal nerve. TNS is commonly delivered by applying stimulating electrodes on the skin of the forehead. The Monarch external

Trigeminal Nerve Stimulation (eTNS) System is being developed to treat several conditions including attention deficit hyperactivity disorder (ADHD), epilepsy, and depression. The Cefaly device is being developed to treat headaches by transcutaneously stimulating the supraorbital and/or infraorbital branches of the trigeminal nerve.

Clinical Evidence

~~Implantable Vagus Nerve Stimulators~~
~~Epilepsy~~
~~Kawai et al. (2017) reported the overall outcome of a national, prospective registry that included all patients implanted in Japan. The registry included patients of all ages with all seizure types who underwent VNS implantation for drug-resistant epilepsy in the first three years after approval of VNS in 2010. The registry excluded patients who were expected to benefit from resective surgery. Efficacy analysis was assessed based on the change in frequency of all seizure types and the rate of responders. Changes in cognitive, behavioral and social status, quality of life (QOL), antiepileptic drug (AED) use, and overall AED burden were analyzed as other efficacy indices. A total of 385 patients were initially registered. Efficacy analyses included data from 362 patients. Age range at the time of VNS implantation was 12 months to 72 years; 21.5% of patients were under 12 years of age and 49.7% had prior epilepsy surgery. Follow-up rate was >90%, even at 36 months. Seizure control improved over time with median seizure reduction of 25.0%, 40.9%, 53.3%, 60.0%, and 66.2%, and responder rates of 38.9%, 46.8%, 55.8%, 57.7%, and 58.8% at three, six, 12, 24, and 36 months of VNS therapy, respectively. There were no substantial changes in other indices throughout the three years of the study, except for self/family-accessed QOL which improved over time. No new safety issues were identified. The authors concluded that this prospective national registry of patients with drug-resistant epilepsy, with > 90% follow-up rate, indicates long-term efficacy of VNS therapy which increased over time, over a period of up to three years.~~

~~Englot et al. (2016) examined rates and predictors of seizure freedom with VNS. The investigators examined 5554 patients from the VNS therapy Patient Outcome Registry, and also performed a systematic review of the literature including 2869 patients across 78 studies. Registry data showed a progressive increase over time in seizure freedom after VNS therapy. Overall, 49% of patients responded to VNS therapy 0 to 4 months after implantation (≥50% reduction seizure frequency), with 5.1% of patients becoming seizure-free, while 63% of patients were responders at 24 to 48 months, with 8.2% achieving seizure freedom. On multivariate analysis, seizure freedom was predicted by age of epilepsy onset >12 years, and predominantly generalized seizure type, while overall response to VNS was predicted by non-lesional epilepsy. Systematic literature review results were consistent with the registry analysis: At 0 to 4 months, 40.0% of patients had responded to VNS, with 2.6% becoming seizure-free, while at last follow-up, 60.1% of individuals were responders, with 8.0% achieving seizure freedom.~~

~~In a Cochrane review, Panebianco et al. (2015) evaluated the current evidence for the efficacy and tolerability of vagus nerve stimulation when used as an adjunctive treatment for people with drug-resistant partial epilepsy. Five randomized controlled trials (439 participants) were included in the review. The authors concluded that VNS for partial seizures appears to be an effective and well tolerated treatment in 439 included participants from five trials. Results of the overall efficacy analysis show that VNS stimulation using the high stimulation paradigm was significantly better than low stimulation in reducing frequency of seizures. Results for the outcome "withdrawal of allocated treatment" suggest that VNS is well tolerated as withdrawals were rare. Adverse effects associated with implantation and stimulation were primarily hoarseness, cough,~~

~~dyspnea, pain, paresthesia, nausea and headache, with hoarseness and dyspnea more likely to occur on high stimulation than low stimulation.~~

~~In the PuLsE trial, Ryvlin et al. (2014) compared outcomes between patients receiving best medical practice (BMP) alone, and those treated with VNS in addition to BMP (VNS+BMP). In a randomized group of 96 patients, significant between-group differences in favor of VNS + BMP were observed regarding improvement in health-related quality of life, seizure frequency, and Clinical Global Impression-Improvement scale (CGI-I) score. More patients in the VNS + BMP group (43%) reported adverse events (AEs) versus BMP group (21%), a difference reflecting primarily mostly transient AEs related to VNS implantation or stimulation. According to the authors, this data suggests that VNS as a treatment adjunct to BMP in patients with pharmacoresistant focal seizures was associated with a significant improvement in health-related quality of life compared with BMP alone.~~

~~In a 2012 clinical guideline for the diagnosis and management of epilepsy, the National Institute for Health and Care Excellence (NICE) stated that vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults, children, and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes adults, children and young people whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures (NICE 2012, Updated April 2018).~~

~~LivaNova is currently recruiting for a feasibility clinical trial for Microburst VNA for the treatment of drug-resistant epilepsy. The new "microburst" feature involves stimulation being delivered in higher frequency bursts rather than at gradual intervals. The trial is not expected to be completed until 2021. (NCT03446664) Refer to the following website for more information: https://clinicaltrials.gov/ct2/show/NCT03446664. (Accessed November 17, 2020)~~

Implantable Vagus Nerve Stimulators

Responsive Vagus Nerve Stimulation Implants (Closed Loop Technology)

There is insufficient evidence to support the use of responsive vagus nerve stimulation implants (closed loop technology) that allow detection and stimulation of increased heart rate (e.g., AspireSR™ Model 106, SenTiva™ Model 1000) for treating epilepsy due to study limitations. Selection criteria and predictors of benefit have not been established. Larger studies are needed to establish safety, efficacy and long-term outcomes.
~~There is insufficient evidence to support the use of the AspireSR for vagus stimulation due to study limitations. Larger studies are needed to establish safety, efficacy and long-term outcomes.~~

Tzadok et al. (2019) in a retrospective review looked at the outcomes in an attempt to understand the long-term effects and therapy benefit of the AspireSR® in a patient population managed in a pediatric neurology unit. The records of patients who underwent transplantation during 2015-2017 and are continuously followed in one pediatric-epilepsy clinic, were retrospectively analyzed. Collected information included demographics, use of antiepileptic drugs and seizure type, frequency and duration before and after VNS implantation. There were 46 patients ages 5-31 years (mean 15.7 ± 5.8), mean age at implantation
14 ± 5.8 years, were included. 29 patients (63%) were new insertions and 17 of the patients (37%) underwent a VNS replacement to the AspireSR® model. Mean follow-up was 13 ± 7.5 months (range 2-29 months). The total cohort responder rate (patients with ≥ 50% reduction in seizure frequency compared to the pre-implantation period) was 60.9%. (62% in the new insertion group; while 59% in the replacement group had additional benefit

over their former VNS model, p = 0.981). Epilepsy etiology, age, age at implantation and type of seizures pre-implantation showed no correlation to response-rate. Five patients (10.9%) experienced complete seizure-freedom following implantation (4/5 in the "new insertion" group). Responses were reported at median follow up of 5 ± 1.3 months post-implantation. 67.4% experienced shorter seizure duration post-implantation. Study limitations included: a small sample-size and by its retrospective design this study was predisposed to biases, including recall-bias of the caregivers as well as selection bias resulting from lack of randomization and data was limited due to the study not being preplanned with gathering the same information or at the same time intervals. While this study provides early and meaningful benefits to drug-resistant epilepsy patients, additional research is needed to include large-scale prospective studies, using standardized seizure-information collection methods and device management data, can provide a more accurate estimate of the device efficacy and overall effect on patient well-being.

Hamilton et al. (2018) compared the efficacy of AspireSR to preceding VNS battery models for battery replacements, and evaluated the efficacy of the AspireSR for new implants. Data were collected retrospectively from patients with epilepsy who had VNS AspireSR implanted over a three-year period between June 2014 and June 2017 by a single surgeon. Cases were divided into two cohorts, those in whom the VNS was a new insertion, and those in whom the VNS battery was changed from a previous model to AspireSR. Within each group, the seizure burden was compared between the periods before and after insertion of AspireSR. Fifty-one patients with a newly inserted AspireSR VNS model had a significant reduction in seizure frequency, with 59% (n = 30) reporting ≥50% reduction. Of the 62 patients who had an existing VNS, 53% (n = 33) reported ≥50% reduction in seizure burden when the original VNS was inserted. After the battery was changed to the AspireSR, 71% (n = 44) reported a further reduction of ≥50% in their seizure burden. The size of this reduction was at least as large as that resulting from the insertion of their existing VNS in 98% (61/62) of patients. The authors indicated that the results suggest that approximately 70% of patients with existing VNS insertions could have significant additional benefit from cardiac based seizure detection and closed loop stimulation from the AspireSR device. According to the authors, this study was a retrospective analysis and they reported patients' and carers' interpretation of their response to VNS therapy rather than by prospectively collected seizure diaries or a formal quality of life assessment tool. This retrospective seizure reporting was therefore a potential source of recall bias. The authors indicated that the lack of blinding and randomization could have resulted in selection bias as patients who were more likely to have had benefit from VNS therapy were offered treatment with AspireSR.

Fisher et al. (2016) evaluated the performance, safety of the Automatic Stimulation Mode (AutoStim) feature of the Model 106 Vagus Nerve Stimulation (VNS) Therapy System during a 3-5-day Epilepsy Monitoring Unit (EMU) stay and long- term clinical outcomes of the device stimulating in all modes. This study was a prospective, unblinded, U.S. multisite study of the AspireSR in patients with drug-resistant partial onset seizures and history of ictal tachycardia. VNS Normal and Magnet Modes stimulation were present at all times except during the EMU stay. Outpatient visits at 3, 6, and 12 months tracked seizure frequency, severity, quality of life, and adverse events. Twenty implanted patients (ages 21-69) experienced 89 seizures in the EMU. A total of 28/38 (73.7%) of complex partial and secondarily generalized seizures exhibited ≥20% increase in heart rate change. A total of 31/89 (34.8%) of seizures were treated by Automatic Stimulation on detection; 19/31 (61.3%) seizures ended during the stimulation with a median time from stimulation onset to seizure end of 35 sec. Mean duty cycle at six-months increased from 11% to 16%. At 12 months, quality of life and seizure severity scores improved, and responder rate

was 50%. Common adverse events were dysphonia (n=7), convulsion (n=6), and oropharyngeal pain (n=3). The authors concluded that the Model 106 performed as intended in the study population, was well tolerated and associated with clinical improvement from baseline. The study design did not allow determination of which factors were responsible for improvements. Study limitations include small sample size (20 patients) and short duration of follow-up (12 months).

Boon et al. (2015) investigated the performance of a cardiac-based seizure detection algorithm (CBSDA) that automatically triggers VNS. Thirty-one patients with drug resistant epilepsy were evaluated in an epilepsy monitoring unit (EMU). Sixty-six seizures (n=16 patients) were available from the EMU for analysis. In 37 seizures (n=14 patients) a ≥20% heart rate increase was found and 11 (n=5 patients) were associated with ictal tachycardia (iTC). Multiple CBSDA settings achieved a sensitivity of ≥80%. False positives ranged from 0.5 to 7.2/hour. A total of 27/66 seizures were stimulated within ± 2 min of seizure onset. In 10/17 of these seizures, where triggered VNS overlapped with ongoing seizure activity, seizure activity stopped during stimulation. Physician-scored seizure severity (NHS3-scale) showed significant improvement for complex partial seizures (CPS) at EMU discharge and through 12 months. Patient-scored seizure severity (total SSQ score) showed significant improvement at 3 and 6 months. Quality of life (QOL) showed significant improvement at 12 months. The responder rate at 12 months was 29.6% (n=8/27). Safety profiles were comparable to prior VNS trials. The authors concluded that the investigated CBSDA has a high sensitivity and an acceptable specificity for triggering VNS. According to the authors, despite the moderate effects on seizure frequency, combined open- and closed-loop VNS may provide valuable improvements in seizure severity and QOL in refractory epilepsy patients. The significance of this study is limited by small sample size and short follow-up period. This study was sponsored by Cyberonics, Inc., the manufacturer of AspireSR.

~~Professional Societies~~

~~American Academy of Neurology (AAN)~~

~~In a practice parameter update on vagus nerve stimulation for epilepsy, the AAN stated that VNS is indicated for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies. The degree of improvement in seizure control from VNS remains comparable to that of new antiepileptic drugs (AEDs) but is lower than that of mesial temporal lobectomy in suitable surgical resection candidates. Because VNS rarely causes complete seizure remission, and is moderately invasive and expensive, use of VNS is more appropriate in individuals unable to tolerate or benefit from antiepileptic drugs (AEDs), and for whom a partial reduction in seizure frequency will significantly improve their quality of life. Sufficient evidence exists to rank VNS for epilepsy as effective and safe, based on a preponderance of Class I evidence (Fisher, 1999).~~

~~In an evidence based guideline update on vagus nerve stimulation for the treatment of epilepsy (Morris et al. 2013), the AAN makes the following recommendations in addition to those reported in the 1999 assessment:~~

- ~~VNS may be considered as adjunctive treatment for children with partial or generalized epilepsy (level C). VNS was associated with a greater than 50% reduction in seizure frequency in 55% of 470 children with partial or generalized epilepsy (14 class III studies) but there was significant heterogeneity in the data.~~

- ~~VNS may be considered in patients with Lennox-Gastaut syndrome (LGS) (level C). VNS was associated with a greater than 50% seizure reduction in 55% of 113 patients with LGS (4 class III studies).~~
- ~~VNS may be considered progressively effective in patients over multiple years of exposure (level C).~~
- ~~There should be extra vigilance in monitoring for occurrence of site infection in children. There is evidence of an increase in infection risk at the VNS implantation site in children relative to that in adults.~~

~~The AAN defines level C as possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. Level C rating requires at least one Class II study or two consistent Class III studies.~~

~~International League Against Epilepsy (ILAE)~~

~~A taskforce by the ILAE defines drug resistant epilepsy as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al., 2010; Téllez-Zenteno et al., 2014).~~

~~Epilepsy Society~~

~~In a vagus nerve stimulation (VNS) therapy factsheet, the Epilepsy Society states that VNS therapy is usually considered if an individual has tried a number of anti-epileptic drugs which have not fully controlled the seizures, and the individual is not suitable for or does not want to have brain surgery (Epilepsy Society, 2016).~~

Depression

There is insufficient evidence to support the use of vagus nerve stimulation for depression due to study limitations. Larger studies are needed to establish safety, efficacy and long-term outcomes.

Bottomley et al. (2020) conducted a systematic review and meta-analysis to provide an update of all studies of adjunctive Vagus nerve stimulation (VNS) in treatment resistant depression (TRD), including recent long-term patient-relevant findings. A recent 5-year comparative study prompted this review of its impact in this very severe population. Previous systematic literature reviews (SLR) cited concerns in terms of missing studies or patient duplication. This review looked at these criticisms, assessed all outcomes of longer-term adjunctive VNS in all studies, irrespective of TRD severity, comparing where feasible with treatment-as-usual (TAU). We searched for adult VNS+TAU studies (January 1, 2000 to June 24, 2019). Comparative and single-arm studies were eligible. All reported efficacy, safety and quality of life (QOL) outcomes were assessed. Where possible, meta-analysis was used to calculate overall pooled effect estimates across studies at several time points. Of 22 identified studies, there were two randomized controlled (RCT), sixteen single-arm and four non-randomized comparative studies. Numerous depression-specific, safety and quality of life (QOL) measures were reported. Meta-analysis was possible for three efficacy [Montgomery-Asberg Depression Rating Scale, Clinician Global Impression-Improvement, Hamilton Rating Scale for Depression] and three safety [serious adverse events, study drop-outs and all-cause mortality] but no QOL measures. Data beyond 2 years was not poolable. Analyses demonstrated that antidepressant benefits improved to 24 months and safety issues were minimal. Heterogeneity was high and statistically significant. There are study limitations. The major limitation was the unavailability of randomized controlled studies and the fact that the available studies did not report the

scope of this review. Despite limitations in the evidence base, the comprehensive summary of VNS+TAU outcomes suggest that this treatment shows improving benefit and hope for this very hard-to-treat chronic population. Future studies are needed that involve data collection of QOL outcomes together with more comprehensive safety and efficacy outcomes, especially for TAU alone, with a view to signal the different treatment combinations.

Aaronson et al. (2017) investigated whether adjunctive vagus nerve stimulation (VNS) with treatment as usual in depression has superior long-term outcomes compared with treatment as usual only. This 5-year, prospective, open-label, nonrandomized, observational Treatment-Resistant Depression Registry study was conducted at 61 U.S. sites and included 795 patients who were experiencing 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). Patients with a history of psychosis or rapid-cycling bipolar disorder were excluded. The primary efficacy measure was response rate, defined as a decrease of ≥50% in baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score at any post-baseline visit during the 5-year study. Secondary efficacy measures included remission. Patients had chronic moderate to severe depression at baseline. The registry results indicate that the adjunctive VNS group 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%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). A sub analysis demonstrated that among patients with a history of response to ECT, those in the adjunctive VNS group had a significantly higher 5-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%). A similar significant response differential was observed among ECT non-responders (59.6% compared with 34.1%). According to the authors, this registry represents the longest and largest naturalistic study of efficacy outcomes in treatment-resistant depression, and it provides additional evidence that adjunctive VNS has enhanced antidepressant effects compared with treatment as usual in this severely ill patient population. The authors indicted there were several important limitations to this registry design. Given ethical concerns about following such a severely ill patient population over a 5-year period, the registry had a naturalistic, observational design and did not randomly assign patients to the treatment groups. Similarly, the treatment assignment in the registry was not blinded, in part because it would have been unethical to implant a sham device for a long duration in severely ill patients.

Berry et al. (2013) performed a meta-analysis to compare the response and remission rates in depressed patients with chronic treatment-resistant depression (TRD) treated with vagus nerve stimulation (VNS) plus treatment as usual (VNS + TAU) or TAU. The six clinical studies included in the meta-analysis were two single-arm studies of VNS + TAU, a randomized trial of VNS + TAU versus TAU, a single arm study of patients who received TAU, a randomized trial of VNS + TAU comparing different VNS stimulation intensities, and a nonrandomized registry of patients who received either VNS + TAU or TAU. Response was based on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions scale's Improvement subscale (CGI-I), as these were the two clinician-rated measures common across all or most studies. Outcomes were compared from baseline up to 96 weeks of treatment with VNS + TAU (n = 1035) versus TAU (n = 425). MADRS response rate for VNS + TAU at 12, 24, 48, and 96 weeks were 12%, 18%, 28%, and 32% versus 4%, 7%, 12%, and 14% for TAU. The MADRS remission rate for VNS + TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14% versus 1%, 1%, 2%, and 4%, for TAU. Adjunctive VNS Therapy was associated with a greater likelihood of response and remission compared with TAU. For patients who had responded to VNS + TAU at 24 weeks, sustained response was more likely at 48 weeks and at 96 weeks. Similar results were observed for CGI-I response. The

authors concluded that for patients with chronic TRD, VNS + TAU has greater response and remission rates that are more likely to persist than TAU. According to the authors, the primary limitation of the meta-analysis involved the individual study designs; namely, that the TAU group data is limited to two trials for the CGI-I scale and one trial for the MADRS scale; in addition, the nonrandomized study and the randomized, sham-controlled study represent the only concurrent head-to-head comparisons of VNS + TAU and TAU.

A Comparative Effectiveness Review was prepared for the Agency for Healthcare Research and Quality (AHRQ) on Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. The report identified only one study (Rush et al., 2005a) comparing VNS to sham, conducted in a Tier 1 major depressive disorder (MDD)/bipolar mix population. According to the AHRQ report, the majority of measures used by this study found no difference between VNS and sham on changes in depressive severity or rates of response and remission. Since only a single study was identified for this comparison, further assessment by key variables was not possible (Gaynes et al., 2011).

In a 2009 guidance document, the National Institute for Health and Care Excellence (NICE) stated that the current evidence on the safety and efficacy of vagus nerve stimulation (VNS) for treatment resistant depression is inadequate in quantity and quality. Therefore this procedure should be used only with special arrangements for clinical governance, consent and audit or research. It should be used only in patients with treatment-resistant depression (NICE, 2009).

Clinical Practice Guidelines

~~Professional Societies~~

American Psychiatric Association (APA)

In a clinical practice guideline for the treatment of patients with major depressive disorder, the APA states that electroconvulsive therapy remains the treatment of best-established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared. The APA states that vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of depression treatment, including ECT [III]. For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression focused psychotherapy but who have shown a response to ECT, maintenance ECT may be considered [III]. Maintenance treatment with VNS is also appropriate for individuals whose symptoms have responded to this treatment modality [III]. According to the APA, relative to other anti-depressive treatments, the role of VNS remains a subject of debate. However, it could be considered as an option for patients with substantial symptoms that have not responded to repeated trials of antidepressant treatment. The three APA rating categories represent varying levels of clinical confidence:

I: Recommended with substantial clinical confidence
II: Recommended with moderate clinical confidence
III: May be recommended on the basis of individual circumstances

(Gelenberg et al., 2010; Reaffirmed October 31, 2015)

Canadian Network for Mood and Anxiety Treatments (CANMAT)

In 2016, the Canadian Network for Mood and Anxiety Treatments (CANMAT) revised the 2009 evidence-based clinical guidelines for the treatment of depressive disorders guidelines by updating the evidence and recommendations. The scope of the 2016 guidelines remains the management of major depressive disorder (MDD) in adults, with a target audience of

psychiatrists and other mental health professionals. Using the question-answer format, the authors conducted a systematic literature search focusing on systematic reviews and meta-analyses. Evidence was graded using CANMAT-defined criteria for level of evidence. Recommendations for lines of treatment were based on the quality of evidence and clinical expert consensus. "Neurostimulation Treatments" is the fourth of six sections of the 2016 guidelines. Evidence-informed responses were developed for 31 questions for 6 neurostimulation modalities: 1) transcranial direct current stimulation (tDCS), 2) repetitive transcranial magnetic stimulation (rTMS), 3) electroconvulsive therapy (ECT), 4) magnetic seizure therapy (MST), 5) vagus nerve stimulation (VNS), and 6) deep brain stimulation (DBS). Most of the neurostimulation treatments have been investigated in patients with varying degrees of treatment resistance. The authors concluded that there is increasing evidence for efficacy, tolerability, and safety of neurostimulation treatments. rTMS is now a first-line recommendation for patients with MDD who have failed at least 1 antidepressant. ECT remains a second-line treatment for patients with treatment-resistant depression, although in some situations, it may be considered first line. Third-line recommendations include tDCS and VNS. MST and DBS are still considered investigational treatments (Milev et al., 2016).

Other Conditions

The use of vagus nerve stimulation has been investigated for other conditions including Alzheimer's disease (Merrill et al., 2006), anxiety (George et al., 2008), autism spectrum disorder (Levy et al., 2010), obsessive-compulsive disorder (Rapinesi et al., 2019), pain (Napadow et al., 2012), headaches (Pintea et al., 2017; Cecchini et al., 2009), sleep disorders (Jain et al., 2014), heart disease/congestive heart failure (De Ferrari et al., 2017; Gold et al. 2016: Zannad et al. 2015; Premchand et al. 2016), asthma (Steyn et al., 2013; Miner et al., 2012), fibromyalgia (Lange et al., 2011), and other psychiatric disorders (Cimpianu et al., 2017). However, because of limited studies, small sample sizes and weak study designs, there is insufficient data to conclude that vagus nerve stimulation is safe and/or effective for treating these indications. Further clinical trials demonstrating the clinical usefulness of vagus nerve stimulation are necessary before it can be considered proven for these conditions.

Transcutaneous (Non-Implantable) Vagus Nerve Stimulation

There is insufficient evidence to support the use of Transcutaneous (Non-Implantable) Vagus Nerve Stimulation due to study limitations. Larger studies are needed to establish safety, efficacy and long-term outcomes.

Cluster Headache

There is insufficient evidence to support the use vagus nerve stimulation for Cluster Headaches due to study limitations. Larger studies are needed to establish safety, efficacy and long-term outcomes.

A Hayes report (2020) for the use of gammaCore (electroCore Medical LLC) noninvasive vagus nerve stimulator for the acute treatment or prevention of episodic and chronic cluster headaches (eCH and cCH) indicates that a small, very-low-quality body of evidence does not allow for conclusions to be drawn regarding the safety and efficacy of nVNS with the gammaCore device for prevention or treatment of CH.

Goadsby et al. (2018) compared non-invasive vagus nerve stimulation (nVNS) with a sham device for acute treatment in patients with episodic or chronic cluster headache (CH) (eCH, cCH). After completing a 1-week run-in period, subjects were randomly assigned (1:1) to receive nVNS or sham therapy during a 2-week double-blind period. 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. The Full Analysis Set comprised 48 nVNS-treated (14 eCH, 34 cCH) and 44 sham-treated (13 eCH, 31 cCH) subjects. For the primary endpoint, nVNS (14%) and sham (12%) treatments were not significantly different for the total cohort. In the eCH subgroup, nVNS (48%) was superior to sham (6%). No significant differences between nVNS (5%) and sham (13%) were seen in the cCH subgroup. Combining both eCH and cCH patients, nVNS was no different to sham. The authors concluded that for the treatment of CH attacks, nVNS was superior to sham therapy in eCH but not in cCH. According to the authors, this study had limitations, including its short duration, which did not allow for evaluation of continued/change in response with long-term nVNS therapy. Another study limitation was the imbalance between CH subtypes, with the eCH subgroup comprising <30% of subjects. During the open-label period, subjects could alter their CH treatment regimens by adding prophylactic therapies, or changing doses of existing treatments, or both. According to the authors, this stipulation confounded the results, making it impossible to discern whether changes in efficacy outcomes were attributable to nVNS therapy or to other changes in treatment during this period.

Gaul et al. (2017) evaluated additional patient-centric outcomes, including the time to and level of therapeutic response, in a post hoc analysis of the PREVA study (Gaul et al., 2016). After a 2-week baseline phase, 97 patients with chronic cluster headache entered a 4-week randomized phase to receive non-invasive vagus nerve stimulation plus standard of care (nVNS + SoC) (n = 48) or SoC alone (n = 49). All 92 patients who continued into a 4-week extension phase received nVNS + SoC. Compared with SoC alone, nVNS + SoC led to a significantly lower mean weekly attack frequency by week 2 of the randomized phase; the attack frequency remained significantly lower in the nVNS + SoC group through week 3 of the extension phase. Attack frequencies in the nVNS + SoC group were significantly lower at all study time points than they were at baseline. Response rates were significantly greater with nVNS + SoC than with SoC alone when response was defined as attack frequency reductions of ≥25%, ≥50%, and ≥75% from baseline. The authors concluded that prophylactic nVNS led to rapid, significant, and sustained reductions in chronic cluster headache attack frequency within 2 weeks after its addition to SoC and was associated with significantly higher ≥25%, ≥50%, and ≥75% response rates than SoC alone. The rapid decrease in weekly attack frequency justifies a 4-week trial period to identify responders to nVNS, with a high degree of confidence, among patients with chronic cluster headache. Of note, the 100% response rate was 8% with nVNS + SoC and 0% with SoC alone. This study examined the prophylactic use of non-invasive vagus nerve stimulation but did not control for placebo effect and lacked data beyond four weeks.

Gaul et al. (2016) evaluated non-invasive vagus nerve stimulation (nVNS) as an adjunctive prophylactic treatment of chronic cluster headache (CH) in a prospective, open-label, randomized study (PREVA Trial) that compared adjunctive prophylactic nVNS (n = 48) with standard of care (SoC) alone (control (n = 49)). A two-week baseline phase was followed by a four-week randomized phase (SoC plus nVNS vs control) and a four-week extension phase (SoC plus nVNS). The primary end point was the reduction in the mean number of CH attacks per week. Response rate, abortive medication use and safety/tolerability were also assessed. During the randomized phase, individuals in the intent-to-treat population treated with SoC plus nVNS (n = 45) had a significantly greater reduction in the number of attacks per week vs controls (n = 48) for a mean therapeutic gain of 3.9 fewer attacks per week. Higher ≥50% response rates were also observed with SoC plus nVNS vs controls. No serious treatment-related adverse events occurred. The authors concluded that adjunctive prophylactic nVNS is a well-tolerated novel treatment for chronic CH, offering clinical

benefits beyond those with standard of care. Study limitations include the lack of a placebo or sham device, an open-label study design, the short treatment duration, and the use of patient-reported outcomes.

Silberstein et al. (2016a) evaluated non-invasive vagus nerve stimulation (nVNS) as an acute cluster headache (CH) treatment. One hundred fifty subjects were enrolled and randomized (1:1) to receive nVNS or sham treatment for ≤1 month during a double-blind phase; completers could enter a 3-month nVNS open-label phase. The primary end point was response rate, defined as the proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. Secondary end points included the sustained response rate (15-60 minutes). Sub-analyses of episodic cluster headache (eCH) and chronic cluster headache (cCH) cohorts were prespecified. The intent-to-treat population comprised 133 subjects: 60 nVNS-treated (eCH, n=38; cCH, n=22) and 73 sham-treated (eCH, n=47; cCH, n=26). A response was achieved in 26.7% of nVNS-treated subjects and 15.1% of sham-treated subjects. Response rates were significantly higher with nVNS than with sham for the eCH cohort (nVNS, 34.2%; sham, 10.6%) but not the cCH cohort (nVNS, 13.6%; sham, 23.1%). Sustained response rates were significantly higher with nVNS for the eCH cohort and total population. Adverse device effects (ADEs) were reported by 35/150 (nVNS, 11; sham, 24) subjects in the double-blind phase and 18/128 subjects in the open-label phase. No serious ADEs occurred. The authors indicated that non-invasive vagus nerve stimulation is a safe and well-tolerated treatment that represents a novel and promising option for eCH. According to the authors, study limitations include the analysis of the cCH cohort as part of the primary end point, the need for careful interpretation of sub-analyses results, challenges with blinding inherent in medical device studies, and the time to first measurement of response used to define the primary efficacy end point.

Migraine Headache

There is insufficient evidence to support the use of the vagus nerve stimulation for migraine headaches due to study limitations. Larger studies are needed to establish safety, efficacy and long-term outcomes.

Diener et al. (2019) conducted a multicenter trial Introduction evaluating non-invasive vagus nerve stimulation (nVNS; gammaCore®) and the potential to prevent migraine days in patients with migraine based on mechanistic rationale and pilot clinical data. The PREMIUM trial (NCT02378844) included a 4-week run-in period, a 12-week double-blind period of randomized treatment with nVNS or sham, and a 24-week open-label period of nVNS. Patients were to administer two 120-second stimulations bilaterally to the neck three times daily (6-8 hours apart). Of the 477 enrolled patients, 332 comprised the intent-to-treat (ITT) population. Mean reductions in migraine days per month (primary outcome) were 2.26 for nVNS (n = 165; baseline, 7.9 days) and 1.80 for sham (n = 167; baseline, 8.1 days) (p = 0.15). Results were similar across other outcomes. Upon observation of suboptimal adherence rates, post hoc analysis of patients with ≥ 67% adherence per month demonstrated significant differences between nVNS (n = 138) and sham (n = 140) for outcomes including reduction in migraine days (2.27 vs. 1.53; p = 0.043); therapeutic gains were greater in patients with aura than in those without aura. Most nVNS device-related adverse events were mild and transient, with application site discomfort being the most common. Results indicated that preventive nVNS treatment in episodic migraine was not superior to sham stimulation in the ITT population. The "sham" device inadvertently provided a level of active vagus nerve stimulation. Post hoc analysis showed significant effects of nVNS in treatment-adherent patients. Study limitations include vagal activity of the sham device, the use of bilateral stimulations

and suboptimal subject adherence to the TID treatment regimen. Future studies are needed that include using an inactive sham device, unilateral stimulation and patients with a higher headache burden.

Tassorelli et al. (2018) evaluated the efficacy, safety, and tolerability of noninvasive vagus nerve stimulation (nVNS; gammaCore; electroCore, LLC,) for the acute treatment of migraine in a multicenter, double-blind, randomized, sham-controlled trial. A total of 248 participants with episodic migraine with/without aura were randomized to receive nVNS or sham within 20 minutes from pain onset. Participants were to repeat treatment if pain had not improved in 15 minutes. nVNS (n = 120) was superior to sham (n = 123) for pain freedom at 30 minutes (12.7% vs 4.2%) and 60 minutes (21.0% vs 10.0%) but not at 120 minutes (30.4% vs 19.7%) after the first treated attack. A post hoc repeated-measures test provided further insight into the therapeutic benefit of nVNS through 30, 60, and 120 minutes. nVNS demonstrated benefits across other endpoints including pain relief at 120 minutes and was safe and well-tolerated. The authors concluded that this randomized sham-controlled trial supports the abortive efficacy of nVNS as early as 30 minutes and up to 60 minutes after an attack. Findings also suggest effective pain relief, tolerability, and practicality of nVNS for the acute treatment of episodic migraine. According to the authors, the role of nVNS in migraine therapy is being further explored in ongoing large-scale, randomized, sham-controlled trials with long-term follow-up.

Silberstein et al. (2016b) evaluated the feasibility, safety, and tolerability of noninvasive vagus nerve stimulation (nVNS) for the prevention of chronic migraine (CM) attacks. In this prospective, multicenter, double-blind, sham-controlled pilot study of nVNS in CM prophylaxis, adults with CM (≥15 headache d/mo) entered the baseline phase (1 month) and were subsequently randomized to nVNS or sham treatment (2 months) before receiving open-label nVNS 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. Fifty-nine participants (mean age, 39.2 years; mean headache frequency, 21.5 d/mo) were enrolled. During the randomized phase, tolerability was similar for nVNS (n = 30) and sham treatment (n = 29). Most adverse events were mild/moderate and transient. Mean changes in the number of headache days were -1.4 (nVNS) and -0.2 (sham). Twenty-seven participants completed the open-label phase. For the 15 completers initially assigned to nVNS, the mean change from baseline in headache days after 8 months of treatment was -7.9. The authors concluded that therapy with nVNS was well-tolerated with no safety issues. Study limitations included the small sample size, blinding challenges, and high discontinuation rate. According to the authors, larger sham-controlled studies are needed.

In a monocentric, randomized, controlled, double-blind study, Straube et al. (2015) assessed the efficacy and safety of transcutaneous stimulation of the auricular branch of the vagal nerve (t-VNS) in the treatment of chronic migraine. After one month of baseline, chronic migraine patients were randomized to receive 25 Hz or 1 Hz stimulation of the sensory vagal area at the left ear by a handhold battery driven stimulator for 4 h/day during 3 months. Headache days per 28 days were compared between baseline and the last month of treatment and the number of days with acute medication was recorded The Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS) questionnaires were used to assess headache-related disability. Of 46 randomized patients, 40 finished the study (per protocol). In the per protocol analysis, patients in the 1 Hz group had a significantly larger reduction in headache days per 28 days than patients in the 25 Hz group. 29.4 % of the patients in the 1 Hz group had a ≥50 % reduction in headache days vs. 13.3 % in the 25 Hz group. HIT-6 and MIDAS scores were significantly improved in both groups, without group differences. There were no serious

treatment-related adverse events. The authors concluded that treatment of chronic migraine by t-VNS at 1 Hz was safe and effective. This study was limited by a small sample size.

The National Institute for Health and Care Excellence (NICE) has published a guideline addressing transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine. The guideline states that current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research (NICE, 2016).

Clinical Practice Guidelines

~~*Professional Societies*~~

American Headache Society (AHS)

The AHS guideline on the treatment of cluster headache does not include specific recommendations for noninvasive vagus nerve stimulation. The guideline notes that future sham-controlled blinded trials are warranted to elucidate the efficacy and safety of nVNS for the treatment of cluster headache (Robbins et al., 2016).

Other Conditions

Transcutaneous vagus nerve stimulation has been investigated for other conditions including atrial fibrillation (Stavrakis et al., 2015), epilepsy (Barbella et al, 2018; Bauer et al., 2016), depression (Liu et al., 2016; Fang et al., 2016; Hein, et al., 2013; Rong, et al., 2016), impaired glucose tolerance (Huang et al., 2014), schizophrenia (Osoegawa et al., 2018), tinnitus (Ylikoski et al., 2017; Kreuzer et al., 2014). Due to limited studies, small sample sizes and weak study designs, there is insufficient data to conclude that transcutaneous vagus nerve stimulation is safe and/or effective for treating these indications. Further clinical trials demonstrating the clinical usefulness of these devices are necessary before it can be considered proven for these conditions.

External or Transcutaneous Trigeminal Nerve Stimulation

There is insufficient evidence to support the use of External or Transcutaneous Trigeminal Nerve Stimulation due to study limitations. Larger studies are needed to establish safety, efficacy and long-term outcomes.

Stanak et al. (2020) performed a systematic review to analyze the effectiveness and safety of the external trigeminal nerve stimulator (eTNS) for the prevention and acute treatment of migraine attacks in episodic and chronic migraine patients. The literature search from four databases that yielded 433 citations and additional seven citations were found via hand-search. Two randomized placebo-controlled trials and five prospective case series were included in the analysis. Results concerning prevention, statistically significant differences were found with respect to reduction of migraine attacks (0.67 less migraine attacks per month), migraine days (1.74 less migraine days per month), headache days (2.28 less headache days per month), and acute antimigraine drug intake (4.24 less instances of acute drug intake per month). Concerning acute treatment, statistically significant differences were found with respect to pain reduction on a visual analogue scale at 1/2/24 h post-acute treatment (1.68/1.02/1.08 improvement, respectively). No serious adverse events happened in any of the studies. E-TNS has the potential to improve migraine symptoms, but the quality of evidence is low. High quality

comparative data, studies with larger sample sizes, and studies with standard and relevant primary outcome parameters are needed.

Gil-López et al. (2020) conducted a randomized controlled trial to determine the long-term efficacy and tolerability of external trigeminal nerve stimulation (ETNS) in patients with focal drug-resistant epilepsy (DRE). Also, to explore whether its efficacy depends on the epileptogenic zone (frontal or temporal), and its impact on mood, cognitive function, quality of life, and trigeminal nerve excitability. Forty consecutive patients with frontal or temporal DRE, unsuitable for surgery, were randomized to ETNS or usual medical treatment. Participants were evaluated at 3, 6 and 12 months for efficacy, side effects, mood scales, neuropsychological tests and trigeminal nerve excitability. Subjects had a median of 15 seizures per month and had tried a median of 12.5 antiepileptic drugs. At 12 months, the percentage of responders was 50% in ETNS group and 0% in control group. Seizure frequency in ETNS group decreased by -43.5% from baseline. Temporal epilepsy subgroup responded better than frontal epilepsy subgroup (55.56% vs. 45.45%, respectively). Median stimulation intensity was 6.2 mA. ETNS improved quality of life, but not anxiety or depression. Long-term ETNS affected neither neuropsychological function, but not trigeminal nerve excitability. No serious side effects were observed. According to the authors, (ETNS is an effective and well-tolerated therapy for focal DRE. Patients with temporal epilepsy responded better than those with frontal epilepsy. Future studies with larger populations are needed to define its role compared to other neurostimulation techniques.

In a systematic review of clinical trials, Reuter et al. (2019) assessed the scientific rigor and clinical relevance of the available data to inform clinical decisions about non-invasive neuromodulation. This analysis compared study designs using recommendations of the International Headache Society for pharmacological clinical trials, the only available guidelines for migraine and cluster headache. Pivotal studies were identified for the three non-invasive neuromodulation therapies with regulatory clearance for migraine and/or cluster headache [i.e., non-invasive vagus nerve stimulation (nVNS), single-transcranial magnetic stimulation (sTMS) and external trigeminal nerve stimulation (e-TNS)]. Therapeutic effects on the pain-free response rate at 2 hours were comparable among the three pivotal studies of acute treatment, with significance (vs sham) demonstrated for sTMS (active, 39%; sham, 22%; p=0.0179) but not for nVNS (active, 30.4%; sham, 19.7%; p=0.067) or e-TNS (active, 19%; sham, 8%; p=0.136). Non-invasive vagus nerve stimulation studies demonstrated the most consistent adherence to available guidelines. The scope of this systematic review was limited by the heterogeneity among the clinical trials analyzed and the unavailability of many of the study results, which precluded a formal systematic meta-analysis of all identified studies. This heterogeneity in the pivotal studies of nVNS, e-TNS, and sTMS makes the comparison of these devices and their efficacy outcomes difficult.

McGough et al. (2019) conducted a blinded sham-controlled trial to assess the efficacy and safety of trigeminal nerve stimulation (TNS) for attention-deficit/hyperactivity disorder (ADHD) and potential changes in brain spectral power using resting-state quantitative electroencephalography. Sixty-two children 8 to 12 years old, with full-scale IQ of at least 85 and Schedule for Affective Disorders and Schizophrenia-diagnosed ADHD, were randomized to 4 weeks of nightly treatment with active or sham TNS, followed by 1 week without intervention. Assessments included weekly clinician-administered ADHD Rating Scales (ADHD-RS) and Clinical Global Impression (CGI) scales and quantitative electroencephalography at baseline and week 4. ADHD-RS total scores showed significant group-by-time interactions. CGI-Improvement scores also favored active treatment. Resting-state quantitative electroencephalography showed increased spectral power in the

right frontal and frontal midline frequency bands with active TNS. The study found that only slightly more than half of those receiving therapy had clinically meaningful improvement and a virtual lack of clinically meaningful adverse events. The authors concluded that this study demonstrates TNS efficacy for ADHD in a blinded sham-controlled trial, with estimated treatment effect size similar to non-stimulants. According to the authors, additional research should examine treatment response durability and potential impact on brain development with sustained use. Chou et al. (2019) assessed the safety and efficacy of external trigeminal nerve stimulation for acute pain relief during migraine attacks with or without aura via a sham-controlled trial. This was a double-blind, randomized, sham-controlled study conducted across three headache centers in the United States. Adult patients who were experiencing an acute migraine attack with or without aura were recruited on site and randomly assigned 1:1 to receive either verum or sham external trigeminal nerve stimulation treatment for 1 hour. Neurostimulation was applied via the e-TNS Cefaly device. Pain intensity was scored using a visual analogue scale (0=no pain to 10=maximum pain). The primary outcome measure was the mean change in pain intensity at 1 hour compared to baseline. A total of 106 patients were randomized and included in the intention-to-treat analysis (verum: n=52; sham: n=54). The primary outcome measure was significantly more reduced in the verum group than in the sham group. With regards to migraine subgroups, there was a significant difference in pain reduction between verum and sham for 'migraine without aura' attacks. For 'migraine with aura' attacks, pain reduction was numerically greater for verum versus sham, but did not reach significance. No serious adverse events were reported, and five minor adverse events occurred in the verum group. The authors concluded that one-hour treatment with external trigeminal nerve stimulation resulted in significant headache pain relief compared to sham stimulation and was well tolerated, suggesting it may be a safe and effective acute treatment for migraine attacks. According to the authors, study limitations included the following: there was a small sample size and unbalanced baseline characteristics between the verum and sham groups for migraine type, migraine duration, and prior acute medication use. These differences in baseline characteristics were subsequently accounted for in a post hoc ANCOVA analysis, without modifying the significance of the treatment effect defined by the primary outcome.

Generoso et al. (2019) examined the effects of trigeminal nerve stimulation (TNS) in major depressive disorder (MDD) after a 10-day experimental protocol. This was a randomized, double blind, and sham-controlled phase II study with 24 patients with severe MDD. Patients underwent a 10-day intervention protocol and were assessed with the 17-item Hamilton Depression Rating Scale (HDRS-17) at following three observation points: baseline (T1), after 10 days (T2), and after one month of the last stimulation session (T3). Main clinical outcome analysis of variance (ANOVA) was performed. Patients in the active group presented a mean reduction of 36.15% in depressive symptoms after the stimulation protocol. There was a significant interaction between group and time regarding HDRS-17 scores. Post hoc analyses exhibited a statistically significant difference between active and sham group symptoms at T2 and T3, which highlights the sustained amelioration of depressive symptoms. The authors concluded that this study found improvement of depressive symptoms for patients undergoing a 10-day stimulation protocol of TNS, and this was sustained after one month of follow-up. The authors indicated that the study had several limitations such as a relatively small sample size and no long-term follow-up.

Boon et al. (2018) conducted a systematic review on the currently available neurostimulation modalities primarily with regard to effectiveness and safety for drug-resistant epilepsy (DRE). The authors found that there is insufficient data to support the efficacy of trigeminal nerve stimulation (TNS) for DRE. According to the authors,

additional data collection on potentially promising noninvasive neurostimulation modalities such as TNS is warranted to evaluate its therapeutic benefit and long-term safety.

The National Institute for Health and Care Excellence (NICE) published guidance on the use of a transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine in 2016. The guidance indicates that the evidence on efficacy for this procedure is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

~~Professional Societies~~Clinical Practice Guidelines

American Academy of Pediatrics

The American Academy of Pediatrics (based on the above McGough (2019) updated their clinical practice guideline for the diagnosis, evaluation, and treatment of ADHD in children and adolescents. The revised guideline states that external trigeminal nerve stimulation (eTNS) cannot be recommended as a treatment for ADHD because supporting evidence is sparse and in no way approaches the robust strength of evidence documented for established medication and behavioral treatments for ADHD. (Wolraich et al. 2019)

Additional Search Terms

Neuromodulation, pneumogastric nerve, non-implantable vagus nerve stimulation devices

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Implantable Vagus Nerve Stimulators

The FDA approved the NeuroCybernetic Prosthesis (NCP)® System (Cyberonics, Inc.) in July 1997 (P970003) for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with medically refractory, partial-onset seizures. In 2017, this approval was extended for use in patients 4 years of age and older. Refer to the following websites for more information:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003S207
- http://www.accessdata.fda.gov/cdrh_docs/pdf/p970003.pdf

(Accessed September 6, 2022)

In July 2005, the VNS Therapy™ System (Cyberonics, Inc.) was approved for marketing by the FDA 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 (PMA Supplement 50). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003S050. (Accessed September 6, 2022)

The VNS Therapy System (Cyberonics now known as LivaNova) received initial FDA Premarket Approval (PMA 970003) on July 16, 1997. The original FDA PMA was granted for VNS Therapy system as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years old. Many supplemental approvals have been issued for this system since the original approval. On June 23, 2017, LivaNova received FDA approval (P970003/S207) of its VNS Therapy system for use as an adjunctive therapy in reducing the

frequency of seizures in persons four years of age and older with partial onset seizures that are refractory to antiepileptic medications. Refer to the following websites for more information:

- https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003.pdf
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003

(Accessed September 6, 2022)

The AspireSR Model 106 generator received FDA premarket approval in May 2015 (PMA P970003). The AspireSR is part of Cyberonics's (now known as LivaNova) VNS Therapy System. The AspireSR Model 106 has an additional, optional mode called AutoStim Mode or Automatic Stimulation. This mode monitors and detects tachycardia heart rates, which may be associated with an impending seizure, and automatically delivers stimulation to the vagus nerve. Refer to the following websites for more information:

- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P970003S173
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=353134

(Accessed September 6, 2022)

The Sentiva Model 1000 generator received FDA premarket approval in October 2017 (PMA P970003). The Sentiva is part of LivaNova's VNS Therapy System. The Sentiva Model 1000 has an additional mode called AutoStim Mode or Automatic Stimulation. SenTiva with AutoStim responds to heart rate increases that may be associated with seizures. Refer to the following website for more information:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003S210.
(Accessed September 6, 2022)

The Vivistim Paired VNS System (MicroTransponder, Inc., Austin, TX, USA) is a fully implanted VNS system intended to be paired with traditional rehabilitative exercises to improve upper limb function in patients who have suffered an ischemic stroke. FDA granted PMA to the Vivistim System in August 2021 (P210007). Refer to the following website for more information:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P210007 (Accessed September 6, 2022)

Transcutaneous (Non-Implantable) Vagus Nerve Stimulation Devices

The FDA has cleared gammaCore for the following 3 indications:

- On April 14, 2017, the FDA granted a de novo request that allows the gammaCore® device to be marketed in the U.S. for the treatment of acute pain associated with episodic cluster headache in adults. According to the FDA, the gammaCore Non-invasive Vagus Nerve Stimulator is intended to provide noninvasive vagus nerve stimulation (nVNS) on the side of the neck. The FDA determined that this device should be classified into class II. Refer to the following website for more information:
https://www.accessdata.fda.gov/cdrh_docs/pdf15/den150048.pdf.
- On January 23, 2018, the FDA expanded indications for the gammaCore (electroCore Inc.) noninvasive vagus nerve stimulator to include the acute treatment of pain associated with migraine headaches in adults. Refer to the following website for more information:
https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173442.pdf.
- On November 28, 2018 electroCore Inc. received 510(k) clearance from the FDA for an expanded label for gammaCore (non-invasive vagus nerve stimulator) therapy for adjunctive use for the preventive treatment of cluster headache in adult patients. Refer to the following website for more information:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K182369.
(Accessed September 6, 2022)

- On March 26, 2020 the FDA granted 510(k) premarket notification to Electrocore for the gammaCore Sapphire. An external vagal nerve stimulator for headache, Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K191830.pdf (Accessed September 7, 2022)

External or Transcutaneous Trigeminal Nerve Stimulation

The FDA granted a de novo classification for the Monarch external Trigeminal Nerve Stimulation (eTNS) System on April 19, 2019. According to the FDA, this device is indicated to treat attention deficit hyperactivity disorder (ADHD) in patients aged 7 to12 years who are not currently taking prescription ADHD medication. The device is used for patient treatment by prescription only and is intended to be used in the home under the supervision of a caregiver during periods of sleep. Refer to the following for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180041.pdf. (Accessed September 6, 2022)

The FDA cleared Cefaly for marketing under the 510(k) de novo process in March 2014. According to the FDA, the Cefaly device is indicated for the prophylactic treatment of episodic migraine in patients 18 years of age or older. On September 15, 2017, the FDA cleared the Cefaly Acute device as substantially equivalent to the predicate device (Cefaly) for use during an acute migraine attack with or without aura. Refer to the following for more information:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN120019
- https://www.accessdata.fda.gov/cdrh_docs/pdf12/K122566.pdf
- https://www.accessdata.fda.gov/cdrh_docs/reviews/K122566.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171446.pdf

(Accessed September 6, 2022)

To locate marketing clearance information for a specific device or manufacturer, search the Center for Devices and Radiological Health (CDRH) 510(k) database or the Premarket Approval (PMA) database by product and/or manufacturer name.

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Policy History/Revision Information

Date	Summary of Changes

TBD	**Coverage Rationale** ***Vagus Nerve Stimulators*** • Removed language indicating implantable vagus nerve stimulators are proven and medically necessary for treating epilepsy in individuals with all of the following: ○ Medically refractory epileptic seizures with failure of two or more trials of single or combination antiepileptic drug therapy or intolerable side effects of antiepileptic drug therapy ○ The individual is not a candidate for epilepsy surgery, has failed epilepsy surgery, or refuses epilepsy surgery after Shared Decision Making discussion ○ No history of left or bilateral cervical vagotomy; the U.S. Food and Drug Administration (FDA) identifies a history of left or bilateral cervical vagotomy as a contraindication to vagus nerve stimulation **State Specific Criteria** • Added language to indicate: ○ Consideration shall be given for Medicaid reimbursement for implantation of the vagus nerve stimulator (VNS) if the treatment is considered medically necessary, the recipient meets the published criteria, and the recipient has a diagnosis of medically intractable epilepsy ○ The following criteria are used to determine recipient eligibility and approval of the VNS: ▪ Partial epilepsy confirmed and classified according to the International League Against Epilepsy (ILAE) classification – The recipient may also have associated generalized seizures, such as tonic, tonic-clonic, or atonic – The VNS may have efficacy in primary generalized epilepsy as well ▪ Age 12 years or older, although case by case consideration may be given to younger children who meet all other criteria and have sufficient body mass to support the implanted system ▪ Seizures refractory to medical anti-epilepsy treatment, with adequately documented trials of appropriate standard and newer anti-epilepsy drugs or documentation of recipient's inability to tolerate these medications ▪ Recipient has undergone surgical evaluation and is considered not to be an optimal candidate for epilepsy surgery ▪ Recipient is experiencing at least four to six identifiable partial onset seizures each month – Recipient must have had a diagnosis of intractable epilepsy for at least two years; the two-year period may be waived if waiting would be seriously harmful to the recipient ▪ Recipient must have undergone quality of life (QOL) measurements; the choice of instruments used for the QOL measurements must assess quantifiable measures of daily life in addition to the occurrence of seizures ▪ In the expert opinion of the treating physician, there must be reason to believe that QOL will improve as a result of implantation of the VNS:

Date	Summary of Changes
	– This improvement should occur in addition to the benefit of seizure frequency reduction – The treating physician must document this opinion clearly in the request for prior authorization (PA) ***Exclusion Criteria*** ○ Regardless of the criteria for recipient selection, authorization for VNS implantation shall not be given if the recipient has one or more of the following criteria: ▪ Psychogenic seizures or other non-epileptic seizures ▪ Insufficient body mass to support the implanted system ▪ Systemic or localized infections that could infect the implanted system ▪ A progressive disorder contraindicated to VNS implantation, e.g., malignant brain neoplasm, Rasmussen's encephalitis, Landau-Kleffner syndrome and progressive metabolic and degenerative disorders **Non-State Specific Criteria** • Revised list of conditions which are unproven and not medically necessary for treating with implantable vagus nerve stimulators; added: ○ Autoimmune disorders ○ Musculoskeletal disorders ○ Upper limb impairment related to stroke • Revised list of unproven and not medically necessary devices: added "responsive vagus nerve stimulation implants (closed loop technology) that allow detection and stimulation based upon increased heart rate (e.g., AspireSR™ Model 106, SenTiva™ Model 1000) for treating epilepsy" ***Trigeminal Nerve Stimulators*** • Removed language indicating transcutaneous (non-implantable) vagus nerve stimulation (e.g., gammaCore® for headaches) for preventing or treating all indications are unproven and not medically necessary due to insufficient evidence of efficacy **Applicable Codes** • Added CPT/HCPCS codes 61886, K1016, K1017, and K1020 • Added notation to indicate CPT/HCPCS codes 64553, K1016, K1017, K1020, L8679, L8680, L8682, L8683, L8685, L8686, L8687, and L8688 are not on the State of Louisiana Fee Schedule and therefore are not covered by the State of Louisiana Medicaid Program **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS129LA.L

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the

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