



# Cigna Medical Coverage Policy

Effective Date ..... 10/15/2014  
Next Review Date ..... 10/15/2015  
Coverage Policy Number ..... 0350

Subject **Vagus Nerve Stimulation (VNS)**

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## Coverage Policy

Cigna covers vagus nerve stimulation (VNS) with an implantable vagus nerve stimulator as medically necessary for the treatment of medically intractable seizures when there is failure, contraindication or intolerance to all suitable medical and pharmacological management.

Cigna covers the replacement/revision of an implantable vagus nerve stimulator and/or leads as medically necessary in an individual that has met the above criteria.

Cigna does not cover VNS with an implantable vagus nerve stimulator for any other indication including, but not limited to, refractory depression because it is considered experimental, investigational or unproven.

Cigna does not cover transcutaneous vagus nerve stimulation (tVNS) for any indication because it is considered experimental, investigational or unproven.

## General Background

### Implantable Vagus Nerve Stimulator for Vagus Nerve Stimulation (VNS)

Vagus nerve stimulation (VNS) therapy has been marketed in the United States for the treatment of partial epilepsy and has been proposed for the treatment of patients with intractable depression. VNS involves the implantation of a generator that stimulates the vagus nerve, one of 12 pairs of cranial nerves (Privitera, 2010). The procedure is performed under general anesthesia by a neurosurgeon who implants the device in the upper

left area of the chest, with a connecting wire that runs under the skin from the device to the vagus nerve in the left side of the neck. Leads are then attached to the nerve. Following this procedure, the generator is programmed to stimulate the vagus nerve at a rate determined by the patient and physician (Heck, 2002).

There are potential mechanical complications related to the surgical implantation of the device. The pulse generator and/or lead can move or come through the skin. Also, the lead can break or become disconnected from the pulse generator. According to the manufacturer, the battery in the VNS pulse generator can last from 1 to 16 years. The lifespan depends on pulse generator model, settings the physician chooses and interaction of the lead and vagus nerve over time. When the battery in the pulse generator runs out, the pulse generator is replaced in order to continue VNS therapy. Replacement or removal of the lead is a different procedure. It is not required for routine replacement of the pulse generator (Cyberonics, 2014).

**U.S. Food and Drug Administration (FDA)—Seizures:** The NeuroCybernetic Prosthesis (NCP) System<sup>®</sup> (Cyberonics, Inc., Webster, TX) was approved by the U.S. Food and Drug Administration (FDA) in 1997 for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over age 12 with medically refractory, partial-onset seizures. Since the original approval, there have been a number of modifications to the device, the instruments used to implant the electrodes, the stimulator, and the software used to control and program the stimulator.

**Literature Review—Seizures:** Evidence in the peer-reviewed scientific literature have shown that VNS may be a viable option to reduce the severity and shorten the duration of seizures in those patients who remain refractory despite optimal drug therapy or surgical intervention, as well as in those with debilitating side effects of antiepileptic medications. Seizure frequency is usually reduced by 50%, which is similar to the result of many drugs but without the side effects. Most patients are not seizure-free after treatment with VNS. More recent studies have investigated the efficacy of VNS as an adjunct therapy for those epileptics with generalized seizures and for children. There is evidence that the use of VNS may provide significant health benefits for refractory pediatric patients and generalized seizures (Ryvlin, et al., 2014; Gasco, et al., 2012; Klinkenberg, et al., 2012; Privitera, et al., 2010; Ardesch, et al., 2007; De Herdt, et al., 2007; You, et al., 2007; Nei, et al., 2006; DeGiorgio et al., 2005; Hui et al., 2004; Buoni, et al., 2004; National Institute for Clinical Excellence (NICE), 2004; Smyth, et al., 2003; Labar et al., 2003; DiGiorgio, et al., 2002; Zamponi, et al., 2002).

**Professional Societies/Organizations—Seizures:** The American Academy of Neurology (AAN) evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy evaluates the evidence since the 1999 assessment regarding efficacy and safety of vagus nerve stimulation (VNS) for epilepsy. The recommendations state, "VNS may be considered for seizures in children, for Lennox-Gastaut syndrome (LGS)-associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C). Children should be carefully monitored for site infection after VNS implantation" Level C is classified as possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. The authors recommendations for further research state that more information is needed on the treatment of primary generalized epilepsy in adults, more information is needed about parameter settings (e.g., cycle time length) would potentially help with better VNS management and use, techniques to reduce infection risk at the VNS site in children should be developed and further information is needed on the effects of VNS on sleep apnea (Morris, et al., 2013).

In the opinion of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) (Fisher, et al., 1999), the VNS population studied in pivotal trials was refractory to standard therapy and may, therefore, present a particular challenge to new therapies. Efficacy of VNS in less severely affected populations remains to be evaluated. Nevertheless, sufficient evidence exists to rank VNS for epilepsy as effective and safe, based on a preponderance of Class I evidence (Fisher et al., 1999). This statement was reaffirmed in 2003.

### **VNS Treatment for Depression**

There are currently three major treatment modalities for which there is substantial evidence of effectiveness in the treatment of a major depressive episode (MDE): pharmacotherapy with antidepressant drugs (ADDs), specific forms of psychotherapy (e.g., cognitive behavior and interpersonal therapy), and electroconvulsive therapy (ECT). ADDs are the usual first-line treatment for depression. Clinical trials have demonstrated efficacy for a number of pharmacologic classes of ADDs. Physicians usually reserve ECT for treatment-resistant cases or when they determine a rapid response to treatment is desirable. For those patients who do not respond to

initial antidepressant treatment, physicians generally use one or more of the following strategies: 1) switching to an alternative first-line ADD; 2) switching to a second line ADD; 3) adding psychotherapy, a second ADD, or all-augmentation agent (not generally considered to have significant antidepressant activity when administered alone). Additional options for treatment-resistant patients, especially for patients who fail on the above alternatives, include monoamine oxidase inhibitors and ECT. For treatment-resistant cases that exhibit a marked seasonal pattern, adding phototherapy to pharmacotherapy may also be an option (FDA, 2005). VNS is being investigated as an adjunctive therapy for treatment resistant depression. It has been proposed that the impulses from the generator are transmitted to the mood centers in the brain to achieve the therapeutic effects against depression. Currently, the precise mechanism of how VNS might enhance mood remains unknown (ECRI, 2010).

**U.S. Food and Drug Administration (FDA)—Depression:** In July 2005, the system received FDA premarket approval (PMA) with limitations. The VNS Therapy System was approved to be used to treat depression for the following indications: “the VNS Therapy System is indicated 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 FDA limitations stated that post-approval studies must be conducted to further characterize the optimal stimulation dosing and patient selection criteria (FDA, 2005).

**Literature Review—Depression:** Studies supporting the use of the vagus nerve stimulation (VNS) System in subjects with treatment-resistant depression (TRD) include: a feasibility trial (Rush, et al., 2000) (referred to in the FDA summary of safety and effectiveness data documentation as D-01); a randomized, sham-controlled three-month clinical trial (Carpenter, et al., 2004; Rush et al., 2005a) (referred to in the FDA summary of safety and effectiveness data documentation as D-02, acute); a long-term (12- and 24-month) open-label extension (Rush, et al., 2005b) (referred to in the FDA summary of safety and effectiveness data documentation as D-02, long-term); and a long-term (12-month) observational study of subjects receiving standard-of-care treatments (D-04) for comparison to D-02 long-term (George, et al., 2005) (referred to in the FDA summary of safety and effectiveness data documentation as the D-02/D-04 comparison study) (FDA, 2005). These studies are outlined below. Although some studies suggest that VNS may be effective for resistant depression, a random-controlled trial did not find a statistically significant difference between sham and active VNS (Rush, et al., 2005a, Rush, et al., 2005b). Long-term, controlled trials and additional studies designed to identify patient selection criteria are needed. The current available evidence is insufficient to permit conclusions regarding the efficacy and safety of VNS as an adjunct therapy in TRD and bipolar disorder.

In a case series study, Cristancho et al. (2011) reported the outcomes of depressed patients treated with VNS. A total of 15 patients with treatment-resistant major depressive episodes, including 10 with major depressive disorder and five with bipolar disorder (DSM-IV criteria), were implanted with a VNS device. Existing antidepressant treatment remained fixed as far as clinically possible. The primary outcome was change from baseline in the Beck Depression Inventory (BDI) score. Outcomes were assessed at six and 12 months postimplant. The six-month response rates were 21.4%, six-month remission rates 14.3% and one-year response rates were 28.6-43%. This study was limited by small sample size and lack of a comparator group.

In an uncontrolled open-label multicenter European study, Bajbouj et al. (2010) assessed the efficacy and the safety of VNS in 74 patients with TRD. Psychometric measures were obtained after three, 12, and 24 months of VNS. Mixed-model repeated-measures analysis of variance revealed a significant reduction at all the three time points in the 28-item Hamilton Rating Scale for Depression (HRSD28) score, the primary outcome measure. After two years, 53.1% (26/49) of the patients fulfilled the response criteria ( $\geq 50\%$  reduction in the HRSD28 scores from baseline) and 38.9% (19/49) fulfilled the remission criteria (HRSD28 scores  $\leq 10$ ). The proportion of patients who fulfilled the remission criteria remained constant as the duration of VNS treatment increased. Voice alteration, cough, and pain were the most frequently reported adverse effects. Two patients committed suicide during the study; no other deaths were reported. No statistically significant differences were seen in the number of concomitant antidepressant medications. According to the investigators, the results of this two-year open-label trial suggest a clinical response and a comparatively benign adverse effect profile among patients with TRD. The lack of a control group limits the validity of the results of this study. This study extends the findings in the Schlaepfer et al. (2008) study.

Schlaepfer et al. (2008) reported the results of an uncontrolled open-label European study of VNS for TRD (D03) which was conducted to determine if the USA results (D01) could be replicated using a similar study

design in a different patient population with different severity and in a different health-care environment. Seventy-four patients with TRD were enrolled from six European countries. The primary outcome was response rate which was defined as a  $\geq 50\%$  reduction in the 28-item Hamilton Depression Rating Scale (HAMD-28) was measured at baseline, three months and 12 months. The Montgomery-Asberg Depression Rating Scale (MADRS), the Inventory of Depressive Symptomatology Self-Rated (IDS-SR), and adverse events were also assessed at baseline, three months, and 12 months. After three months of VNS, the response rate was 37% and the remission rate (HAMD-28 score  $< 10$ ) was 17%. At one year, the response rate increased to 53% and the remission rate was 33%. Median time to response was nine months. The most frequent side effects were voice alteration and cough. Most of the efficacy ratings were in the same range as those reported in the USA study. At 12 months, however, the reduction of symptoms was significantly higher in the European study. This may be due to the significant difference in baseline measures of depression (HAMD-28) (D03  $34.0 \pm 5.8$  vs. D01  $36.8 \pm 5.8$ ;  $p=0.006$ ). The authors reported that VNS may be effective in patients with very treatment resistant depression, but could not assess the contribution of the placebo effect on the results. The limitations of this study, including lack of control, blinding and randomization, did not allow definitive determinations to be made regarding the safety and efficacy of VNS for TRD at this time.

Corcoran et al. (2006) studied the safety and efficacy of VNS therapy in 11 patients with chronic TRD in an open-label study. Patients were eligible if they had the following: a diagnosis of major depressive disorder; suffered from a chronic ( $> 2$  years) current episode; scored  $\geq 20$  on the Hamilton Rating Scale for Depression (HRSD); and failed to respond to antidepressants from at least two categories. There were two periods studied—the acute phase (12 weeks), which started two weeks after implantation, and the long-term phase (40 weeks). No changes in antidepressant medications were allowed during the acute phase, but changes were allowed during the long-term phase. Patients were rated on three different rating scales: HRSD, Montgomery-Asberg Depression Rating Scale (MADRS), and Inventory of Depressive Symptomatology-Subjective Rating (IDS-SR). Response was defined as a  $\geq 50\%$  decrease in the HRSD from baseline, and remission was defined as an HRSD score  $< 10$ . All three measures of depression were statistically reduced at one year when compared to baseline (HRSD  $p=0.001$ , MADRS  $p=0.013$ , IDS-SR  $p=0.002$ ). There was one responder at three months, two at six months, and six (55%) at one year. Three patients (27%) remitted by one year. Severe adverse events included one suicide (a treatment nonresponder), one patient with multiple occurrences of pulmonary emboli, and two patients with vocal cord palsies. This study suggests that vagus nerve stimulation (VNS) may be an effective treatment for patients with chronic treatment-resistant depression (TRD). Limitation of this study included small sample size, lack of comparison, and the unknown impact of the medication adjustments made during the long-term phase.

In 2005, Nahas and colleagues reported the response and remission rates of a two-year follow-up study of 59 participants with treatment-resistant, nonpsychotic depressive disorders (D-01 study participants). Response was defined as a  $\geq 50\%$  reduction from baseline of the HRSD score, and remission was defined as a Hamilton Rating Scale for Depression (HRSD) score  $\leq 10$ . Changes in treatment, including VNS parameters, medication dose and type, and the use of electroconvulsive therapy were allowed after the 12-week acute phase. Response rates did not significantly increase from 30.5% at three months to 44.1% at 12 months ( $p=.096$ ), nor did they decrease significantly to 42.4% at 24 months ( $p=.648$ ). Remission rates showed a nonsignificant increase from 15.3% at three months to 27.1% at 12 months ( $p=.07$ ) and a nonsignificant decrease to 22.0% from 12 to 24 months ( $p=.549$ ). At 24 months, 48/59 participants (81%) were still receiving VNS. In the 24 months following initiation of stimulation, 40 serious adverse events occurred in 25 participants and included three for suicide attempts, 10 for worsened depression, one for dysphoria, two for a manic episode, one for agitation, and one for central nervous system toxicity. The follow-up data suggests that VNS therapy for treatment-resistant participants may be sustained over a 24-month period. This study is limited by the small sample size, the lack of control and comparator, and the use and changes in concomitant treatments.

Rush et al. (2005a) conducted a randomized, double-blind study (D-02, acute) of patients with treatment-resistant depression at 21 sites. A total of 222 participants were included; 112 were randomized to the active VNS group, and 110 were randomized to the sham VNS group. Inclusion criteria consisted of a current Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) primary diagnosis of major depressive disorder (MDD) or bipolar I or II disorder (BPI or BPII). The participants were required to be in the current major depressive episode (MDE) for  $\geq$  two years or to have had at least four lifetime major depressive episodes, including their current MDE. Results were based on response rates ( $\geq 50\%$  reduction from baseline on the 24-item Hamilton Rating Scale for Depression [HRSD-24]). At ten weeks, the primary outcome, the HRSD-24 response rate, was 15.2% in the active VNS group and 10.0% in the sham group and was statistically

insignificant. There was a statistically significant response in the Inventory of Depressive Symptomatology - Self Report (IDS-SR30), with a 17% response rate in the active VNS group and 7.3% in the sham group. The authors summarized that, although the VNS therapy was well-tolerated, there was no evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression.

Rush et al. (2005b) conducted a 12-month study (D-02, long-term) of the symptomatic outcomes in patients receiving adjunctive VNS. Participants included in this study had been randomized to receive either active or sham VNS during a 12-week acute phase trial (D-02, active) (Rush et al., 2005a). The initial active VNS group received another nine months of VNS, while the initial sham group received 12 months of VNS. In total, there were 205 evaluable participants. The participants received antidepressant treatments and VNS. Changes in type or dose of any psychotropic or other medication as well as the introduction or discontinuation of somatic treatments (e.g., ECT and rTMS) or psychotherapy were allowed. The primary outcome (repeated measures linear regression) showed a reduction in the HRSD-24 scores (average improvement of 0.45 points per month). At conclusion of the study, the HRSD-24 response rate was 27.2%, and remission was 15.8%. The most common were voice alteration, dyspnea, and neck pain. Of the 205 participants, there were three reports of manic syndrome over the 12 months of this study, as well as 30 participants requiring hospitalization for depression. The authors reported that VNS was well-tolerated at one year with a potential benefit, although changes in depression treatments occurred. To determine if these benefits are due to VNS, long-term, comparative studies are needed.

George et al. (2005) reported a one-year comparison study of VNS of patients who had treatment as usual (TAU) for TRD to better understand the effects on long-term outcome (D-02/D04 comparison study). The authors compared 12-month VNS+TAU outcomes to those of a comparable TRD group. Admission criteria were similar for those receiving VNS+TAU (n=205) or only TAU (n=124). In the primary analysis, repeated measures of linear regression were used to compare the VNS+TAU group (monthly data) to the TAU group (quarterly data) according to scores of the 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR 30). The two groups had similar baseline demographic data, psychiatric treatment histories, and degrees of treatment resistance, except that more TAU participants had at least 10 prior MDEs, and the VNS+TAU group had more ECT before study entry. VNS plus TAU was associated with greater improvement per month in IDS-SR (30) than treatment as usual (TAU) across 12 months ( $p < .001$ ). Response rates, according to the 24-item Hamilton Rating Scale for Depression (HRSD) (last observation carried forward) at 12 months, were 27% for vagus nerve stimulation (VNS)+TAU and 13% for TAU ( $p < .011$ ). Both groups received similar TAU (drugs and ECT) during follow-up. The authors reported that the comparison of two similar but nonrandomized treatment-resistant depression (TRD) groups showed that VNS+TAU was associated with a greater antidepressant benefit over 12 months.

Neu et al. (2005) reported a randomized controlled trial conducted to investigate if VNS has an influence on cerebral blood flow (CBF) in humans. This investigation was designed as an add-on study (DO1; Rush, 2000). In 10 patients with an implanted stimulator who participated in a multicenter clinical trial to evaluate the efficacy of VNS in depression, CBF was investigated by functional transcranial Doppler at baseline (before the stimulator was turned on for the first time) and during stimulation with three different stimulation intensities in a randomized order. No significant change of CBF above standard deviation could be registered. The authors reported that VNS does not have an influence on CBF velocity in depressive patients.

Carpenter et al. (2004) (partial results DO2 randomized controlled trial) reported that VNS has shown promising antidepressant effects in TRD, but the mechanisms of action are not known. Cerebrospinal fluid (CSF) studies in epilepsy patients show that VNS alters concentrations of monoamines and gamma aminobutyric acid (GABA), neurotransmitter systems possibly involved in the pathogenesis of depression. Twenty-one adults with treatment-resistant, recurrent, or chronic major depression underwent standardized lumbar puncture for collection of 12 mL CSF on three separate but identical procedure days during participation in the VNS D-02 clinical trial. All subjects remained on stable regimens of mood medications. Collections were made at baseline (two weeks after surgical implantation but before device activation), week 12 (end of the acute-phase study), and week 24. Cerebrospinal fluid concentrations of norepinephrine (NE), 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) were determined with high-performance liquid chromatography. Concentrations of GABA were assayed with mass spectrometry. Comparison of sham versus active VNS revealed a significant (mean 21%) VNS associated increase in CSF HVA. Mean CSF concentrations of NE, 5-HIAA, MHPG, and GABA did not change significantly. Higher baseline HVA/5-HIAA ratio predicted worse clinical outcome. The authors reported that although several of the CSF

neurochemical effects observed in the VNS study were similar to those described in the literature for antidepressants and ECT, the results did not suggest a supposed antidepressant mechanism of action for VNS.

Marangell et al. (2002) reported a nonrandomized, open-label, single-arm study (DO1) of adults in a treatment-resistant major depressive episode (MDE). This open follow-up study was conducted to determine whether the initial promising effects were sustained, and whether changes in function would be observed. Thirty adult outpatients in a treatment-resistant, nonpsychotic MDE received an additional nine months of VNS treatment following exit from the three-month acute study. Changes in psychotropic medications and VNS stimulus parameters were allowed during this longer term follow-up study. A priori definitions were used to define response ( $\geq 50\%$  reduction in baseline HDRS) and remission ( $\text{HDRS} \geq 10$ ). The response rate was sustained (40%–46%;  $p < 0.317$ ) and the remission rate significantly increased (17–29%;  $p < 0.045$ ) with an additional nine months of long-term VNS treatment after exit from the acute study (one year total VNS treatment). Significant improvements in function between acute study exit and the one-year follow-up assessment as measured by the Medical Outcomes Study Short Form-36 were observed. The authors reported that longer term VNS treatment was associated with sustained symptomatic benefit and sustained or enhanced functional status in this follow-up study.

Sackeim et al. (2001b) reported a nonrandomized, open-label, single-arm study of VNS in 60 patients with treatment-resistant MDEs. The study aimed to: 1) define the response rate; 2) determine the profile of side effects; and 3) establish predictors of clinical outcome. Participants (DO-1) were outpatients with nonatypical, nonpsychotic major depressive or bipolar disorder who had not responded to at least two medication trials from different antidepressant classes in the current MDE. While on stable medication regimens, the patients completed a baseline period followed by device implantation. A two-week, single-blind recovery period (no stimulation) was followed by 10 weeks of VNS. Of 59 completers (one patient improved during the recovery period), the response rate was 30.5% for the HRSD measure, 34.0% for the Montgomery-Asberg Depression Rating Scale (MADRAS) and 37.3% for the Clinical Global Impressions-Improvement index (CGI-I). The most common side effect was voice alteration or hoarseness (55.0%, 33/60), which was generally mild and related to output current intensity. History of treatment resistance was predictive of VNS outcome. Patients who had never received ECT (lifetime) were 3.9 times more likely to respond. Of the 13 patients who had not responded to more than seven adequate antidepressant trials in the current major depressive episode (MDE), none responded, compared to 39.1% of the remaining 46 patients ( $p < 0.0057$ ). The author reports vagus nerve stimulation (VNS) appears to be most effective in patients with low to moderate, but not extreme, antidepressant resistance. Given the finding that VNS is unlikely to be successful as a “last resort” treatment, its role in the care of patients with low to moderate levels of treatment resistance will require careful consideration. Evidence concerning the long-term therapeutic benefits of VNS and tolerability will be critical in determining its role in treatment-resistant depression (TRD).

Sackeim et al. (2001a) reported a prospective, nonrandomized, open-label study to determine whether VNS leads to neurocognitive deterioration. A neuropsychological battery was administered to 27 patients (from DO-1) with TRD before and after 10 weeks of VNS. Thirteen neurocognitive tests sampled the domains of motor speed, psychomotor function, language, attention, memory, and executive function. The authors report that no evidence of deterioration in any neurocognitive measure was detected. Relative to baseline, improvement was found in motor speed (i.e., finger tapping), psychomotor function (i.e., digit symbol test), language (i.e., verbal fluency), and executive functions (i.e., logical reasoning, working memory, response inhibition, or impulsiveness). For some measures, improved neurocognitive performance correlated with the extent of reduction in depressive symptoms, but VNS output current was not related to changes in cognitive performance. The authors state that VNS in TRD may result in enhanced neurocognitive function, primarily among patients who show clinical improvement. Controlled investigation is needed to rule out the contribution of practice effects.

Rush et al. (2000) investigated VNS as delivered by the NeuroCybernetic Prosthesis (NCP) System. The open-label nonrandomized, uncontrolled clinical study (D-01) covered 30 adult outpatients with nonpsychotic treatment-resistant major depressive ( $n=21$ ) or bipolar I ( $n=4$ ) or bipolar II ( $n=5$ ) depressed phase disorders, who had failed at least two robust medication trials in the current MDE while on stable medication regimens. The patients completed a baseline period followed by NCP System implantation. A two-week single-blind recovery period (no stimulation) was followed by 10 weeks of VNS. Results indicated that in the current MDEs (median length=4.7 years), patients had not adequately responded to two ( $n=9$ ), three ( $n=2$ ), four ( $n=6$ ) or five or more ( $n=13$ ) robust antidepressant medication trials or ECT ( $n=17$ ). Baseline 28 item Hasegawa's Dementia Scale (HDS) scores averaged 38.0. Response rates ( $\geq 50\%$  reduction in baseline scores) were 40% for both the

HDRS28 and the Clinical Global Impressions-Improvement index (CGI-I) (score of 1 or 2) and 50% for the Montgomery-Asberg Depression Rating Scale (MADRAS). Symptomatic responses (accompanied by substantial functional improvement) have been largely sustained during long-term follow-up to date. The researchers concluded that these open trial results suggest that VNS has antidepressant effects in TRD. This uncontrolled study was small, without long-term outcome and with no comparison group.

In 2012, Martin et al. reported the results of a systematic review and meta-analysis to evaluate the efficacy of VNS for the treatment of depression. Efficacy was evaluated according to severity of illness and percentage of responders. A total of 14 studies met the selection criteria and were included in the review. The results are mainly based on uncontrolled studies, with small or medium sample sizes and intermediate quality levels. The duration of the randomized controlled trial included was 10 weeks. The meta-analysis of efficacy for uncontrolled studies showed a significant reduction in scores at the Hamilton Depression Rating Scale endpoint, and the percentage of responders was 31.8% ([23.2%-41.8%],  $p < 0.001$ ). However, the randomized control trial which covered a sample of 235 patients with depression, reported no statistically significant differences between the active intervention and placebo groups. The authors reported that currently, insufficient data are available to describe VNS as effective in the treatment of depression. Additionally, it cannot be ruled out that the positive results observed in the uncontrolled studies might have been mainly due to a placebo effect.

In 2008, Daban et al. reported the results of a systematic review and meta-analysis to evaluate the safety and efficacy of VNS in TRD. A total of 18 studies were included in the review (six short term and 12 long term studies). Some studies included patients who had already been enrolled in previous studies. Only one study was randomized and therefore, a meta-analysis could not be performed. According to the authors, the current literature suggests that VNS therapy is promising and may have a potential role in the treatment of TRD, but experience and the evidence base are still limited. They also stated that VNS is an invasive treatment involving risk and that although the evidence is weak, it may have a role in the treatment of depressed patients not responding well to medication, particularly those with a chronic, disabling course. The authors reported that large, well-designed studies are needed to confirm the results reported in mainly open studies regarding the efficacy of VNS in major depression.

In the 2011 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review of nonpharmacologic interventions for treatment-resistant depression (TRD) in adults the authors present evidence that provides a comprehensive summary of the available data addressing the comparative effectiveness of four nonpharmacologic treatments as therapies for patients with TRD: electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy or interpersonal psychotherapy (CBT or IPT). The overview states that "the greatest volume of evidence is for ECT and rTMS; however, the direct comparative evidence about even these treatments is quite limited. Available indirect evidence primarily involves rTMS; a little information is available on VNS and psychotherapy (chiefly for efficacy and adverse events), and no available indirect evidence involves ECT. Given the limited number of Tier 1 studies incomplete reporting on the number of failed treatment attempts, we were unable to stratify our outcomes by the number of treatment failures within Tier 1." Tier 1 Evidence (TRD as defined in this report) includes studies in which patients specifically had two or more prior treatment failures with medications (Gaynes, et al., 2011).

**Professional Societies/Organizations—Depression:** The American Psychiatric Association (APA) practice guideline for the treatment of patients with major depressive disorder discusses vagus nerve stimulation (VNS) under other somatic therapies. The authors state that electroconvulsive therapy (ECT) 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. VNS may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant 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 antidepressive 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).

### **Other Indications**

VNS has been proposed for use in a number of other indications including, but not limited to, addiction, Alzheimer's disease, anxiety, autism, bulimia, cerebral palsy, chronic heart failure, coma, craving, essential tremor, fibromyalgia, headache, memory and learning disability, migraine, multiple sclerosis, narcolepsy, obesity, obsessive-compulsive disorder, panic disorder, pain syndromes, posttraumatic stress disorder, sleep disorder, traumatic brain injury, Tourette's Syndrome. In AD, it has been proposed that stimulation of the vagus nerve may cause surges in norepinephrine in an area of the brain that is involved with memory storage (Adelson, 2004). The peer-reviewed scientific literature regarding the use of VNS for AD or other indications is limited by small sample size and lack of a comparator and therefore conclusions about safety and efficacy cannot be made at this time. VNS devices are not FDA-approved for treatment of these indications. (Shi, et al., 2013; McClelland, et al., 2013, ECRI, 2013; Herremans, et al., 2012; Lange, et al., 2011; De Ferrari, et al., 2011; Beekwilder, et al., 2010; Klein; et al., 2010; Levy, et al., 2010; George, et al., 2010; Pardo, et al., 2007; George, et al., 2007; Ansari, et al., 2007; Bodenlos, et al., 2007; Merrill, et al., 2006; Hatton, et al., 2006; Mauskop, et al., 2005; Adelson, 2004; Handforth, et al., 2003; Sjogren, et al., 2002; Marolow, et al., 2001).

### **Transcutaneous Vagus Nerve Stimulator (tVNS)**

Transcutaneous vagus nerve stimulation (tVNS) is being investigated as a noninvasive alternative to surgery for VNS. tVNS involves the stimulation of the superficial branches of the vagus nerve of the ear. Electrodes are placed on the ear and wired to the transcutaneous electrical stimulator (TENS) which is controlled by the patient (Rong, et al., 2012). tVNS has been proposed for use in a number of indications including, but not limited to tinnitus (Lehtimaki, et al., 2013), intractable epilepsy (He, et al., 2013; Stefan, et al., 2012), depression (Hein, et al., 2012; Rong, et al., 2012), pain (Busch, et al., 2013), cardiac function (Kreuzer, et al., 2012), postoperative cognitive dysfunction in elderly patients (Xiong, et al., 2009). Most of the evidence in the peer-reviewed literature for tVNS consists of pilot studies or case series for a variety of indications. The studies are limited by lack of a comparator and small sample size therefore conclusions about safety and efficacy cannot be made at this time.

### **Use Outside of the US**

Per the manufacturer website, in 2011 the tVNS device NEMOS<sup>®</sup> received the European market (CE mark) for the treatment of epilepsies. This device is not FDA-approved in the United States.

In December 2009, the National Institute for Clinical Excellence (NICE) (United Kingdom) published a guidance document addressing vagus nerve stimulation for treatment-resistant depression stating, "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" The authors stated that for efficacy outcomes the interpretation of the evidence was complicated by different publications reporting on the same patients but at different follow-up periods (NICE, 2009).

The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT) partnered to produce evidence-based clinical guidelines for the treatment of depressive disorders. Four forms of neurostimulation for depression were reviewed in the guidelines. Electroconvulsive therapy (ECT) had the most extensive evidence, spanning seven decades. Repetitive transcranial magnetic (rTMS) and vagus nerve stimulation (VNS) have been approved to treat depressed adults in both Canada and the United States with a small evidence base. Compared to other modalities for the treatment of major depressive disorder (MDD), the data based is limited by the relatively small numbers of randomized controlled trials (RCTs) and small sample sizes. The authors concluded that there is the most evidence to support ECT as a first-line treatment under specific circumstances and rTMS as a second-line treatment. The evidence to support VNS is less robust and deep brain stimulation remains an investigational treatment (Kennedy, 2009).

### **Summary**

Although questions remain regarding patient selection criteria and optimal stimulation parameters, there is sufficient evidence regarding the effectiveness and safety of vagus nerve stimulation (VNS) to conclude that VNS may improve health outcomes in patients with medically refractory seizures. There is evidence to support the use of VNS in children and in patients with generalized seizures.

The use of VNS for treatment-resistant depression (TRD) has been considered approvable by the U.S. Food and Drug Administration (FDA), conditional on the conduct of post-market clinical trials. Although some studies suggest that VNS may be effective for resistant depression, a random-controlled trial did not find a statistically significant difference between sham and active VNS (Rush, et al., 2005a, Rush, et al., 2005b). Long-term, controlled trials and additional studies designed to identify patient selection criteria are needed. The current available evidence is insufficient to permit conclusions regarding the efficacy and safety of VNS as an adjunct therapy in TRD and bipolar disorder.

The peer-reviewed scientific literature regarding the use of VNS for Alzheimer's disease or other indications is limited by small sample size and lack of a comparator and therefore conclusions about safety and efficacy cannot be made at this time. The evidence in the published peer-reviewed scientific literature does not support VNS for any of the following conditions (list may not be all inclusive):

- addiction
- Alzheimer's disease
- anxiety
- autism
- bulimia
- cerebral palsy
- chronic heart failure
- coma
- craving
- essential tremor
- fibromyalgia
- headache
- memory and learning disability
- migraine
- multiple sclerosis
- narcolepsy
- obesity
- obsessive-compulsive disorder
- panic disorder
- pain syndromes
- posttraumatic stress disorder
- sleep disorder
- traumatic brain injury
- Tourette's Syndrome

Transcutaneous vagus nerve stimulation (tVNS) is being investigated as a noninvasive alternative to surgery for VNS numerous indications. The studies are limited by lack of a comparator and small sample size therefore conclusions about safety and efficacy cannot be made at this time.

## Coding/Billing Information

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Covered when medically necessary:**

CPT®* Codes	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 two or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or receiver
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Incision for 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

<b>HCPCS Codes</b>	<b>Description</b>
C1767	Generator, neurostimulator (implantable), nonrechargeable
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
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, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

**Experimental/Investigational/Unproven/Not Covered when used to report Transcutaneous Vagus Nerve Stimulation (tVNS):**

<b>CPT* Codes</b>	<b>Description</b>
64550	Application of surface (transcutaneous) neurostimulator

<b>HCPCS Codes</b>	<b>Description</b>
E0720	Tens, two lead, localized stimulation

\*Current Procedural Terminology (CPT®) © 2013 American Medical Association: Chicago, IL.

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