Clinical Policy Bulletin: Vagus Nerve Stimulation

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Policy

Aetna considers vagus nerve electrical stimulators medically necessary durable medical equipment (DME) for shortening the duration or reducing the severity of seizures in members with partial onset seizures who remain refractory to optimal anti-epileptic medications and/or surgical intervention, or who have debilitating side effects from anti-epileptic medications. (Note: Electronic analysis of an implanted neurostimulator pulse generator system for vagus nerve stimulation is considered medically necessary when criteria are met).

Aetna considers transcutaneous vagus nerve stimulation experimental and investigational for the treatment of seizures and all other indications (see below) because the effectiveness of this approach has not been established.

Aetna considers vagus nerve electrical stimulators and transcutaneous vagus nerve stimulation experimental and investigational for the treatment of all other indications because its effectiveness for these indications has not been established (not an all inclusive list):

- Addictions
- Anxiety disorders
- Autism
- Bipolar disorders
- Cerebral palsy
- Chronic headaches
- Cognitive impairment associated with Alzheimer's disease
- Coma
- Depression
- Eating disorders (e.g., anorexia and bulimia)
- Essential tremor
- Fibromyalgia
- Generalized epilepsy syndromes
- Generalized treatment-resistant epilepsy
- Heart failure
- Hemicrania continua
- Impaired glucose tolerance/Pre-diabetes
- Juvenile myoclonic epilepsy
- Migraine headaches
- Mood disorders
- Narcolepsy
- Obesity
- Obsessive-compulsive disorder
Sleep disorder
Stroke
Tinnitus
Tourette's syndrome
Traumatic brain injury (TBI) including post-TBI pneumonia

See also CPB 0221 - Quantitative EEG (Brain Mapping), CPB 0226 - Hospitalization for the Initiation of Ketogenic Diet for the Treatment of Intractable Seizures, CPB 0279 - Magnetic Source Imaging/Magnetoencephalography, CPB 0322 - Electroencephalographic (EEG) Video Monitoring, CPB 0394 - Epilepsy Surgery, CPB 0425 - Ambulatory Electroencephalography, and CPB 0406 - Tinnitus Treatments.

Background

Approximately 1.7 millions Americans suffer from epilepsy. The vast majority of these patients can be controlled by conventional drug therapy. Despite the availability of new anti-epileptic medications and advances in surgical therapy, more than 200,000 people remain refractory to treatment. Vagus nerve stimulation (VNS) using the NeuroCybernetic Prosthesis (NCP) System has been shown to shorten the duration and reduce the severity of seizures in certain patients who remain refractory despite optimal drug therapy or surgical intervention or in those with debilitating side effects of anti-epileptic medications.

The NCP System, approved by the Food and Drug Administration (FDA) on July 16, 1997, is a pacer-like device implanted under the skin in the upper left chest area. It is connected by wire to a lead that is wrapped around the left vagus nerve in the neck. Through the vagus nerve, it delivers intermittent electrical pulses 24 hours a day to the brain. When a patient senses the impending onset of a seizure, he/she can activate the device through a hand-held magnet to deliver an additional dose of stimulation. Treatment with the vagus nerve stimulator is not free of side effects. Patients have experienced cough, hoarseness, alterations in their voice, and shortness of breath.

Recent studies have established vagus nerve stimulation to be a viable option for improving seizure control in difficult to treat pediatric patients with epilepsy (Zamponi et al, 2002; Murphy et al, 2003; Smyth et al, 2003; and Buoni et al, 2004). An assessment of VNS in children by the National Institute for Clinical Excellence (NICE, 2004) reached the following conclusion:

"Current evidence on the safety and efficacy of vagus nerve stimulation for refractory epilepsy in children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance".

It has been reported that VNS in patients with epilepsy is associated with an improvement in mood. Approximately 1/3 of patients with major depressive disorder fail to experience sufficient symptom improvement despite adequate treatment. Management of patients with treatment resistant depression (TRD) usually consists of pharmacological or non-pharmacological methods. The former approach entails switching to another anti-depressant monotherapy, and augmentation or combination with 2 or more antidepressants or other agents. The latter approach includes psychotherapy, electroconvulsive therapy, and VNS. Although VNS is associated with mood improvements in patients with epilepsy, randomized, controlled studies with long-term follow-up are needed to confirm its effect on TRD. In this regard, Kosel and Schlaepfer (2003) stated that recent data from an open-label, multi-center pilot study involving 60 patients (Goodnick et al, 2001) suggested a potential clinical usefulness in the acute and maintenance treatment of TRD. However, definite therapeutic effects of clinical significance remain to be confirmed in large placebo-controlled trial. This is in agreement with the observation of George et al (2000) who noted that additional research is needed to clarify the mechanisms of action of VNS and its potential clinical utility in the management of patients with TRD. Because of the lack of well-designed controlled clinical trials, VNS for refractory
depression is considered experimental and investigational. Long-term data regarding tolerability as well as symptomatic and functional outcomes of depressed patients receiving VNS are needed to ascertain the effectiveness of this procedure for treating refractory depression. An assessment by the Institute for Clinical Systems Improvement (ICSI, 2004) stated that VNS for depression “cannot be considered evidence-based.”

In an acute phase pilot study (n = 59), Nahas et al (2005) evaluated the safety and effectiveness of VNS for patients with treatment-resistant major depressive episode (MDE). They examined the effects of adjunctive VNS over 24 months in this patient population. Adult outpatients with chronic or recurrent major depressive disorder or bipolar (I or II) disorder and experiencing a treatment-resistant, non-psychotic MDE (DSM-IV criteria) received 2 years of VNS. Changes in psychotropic medications and VNS stimulus parameters were allowed only after the first 3 months. Response was defined as greater than or equal to 50 % reduction from the baseline 28-item Hamilton Rating Scale for Depression (HAM-D-28) total score, and remission was defined as a HAM-D-28 score less than or equal to 10. Based on last observation carried forward analyses, HAM-D-28 response rates were 31 % (18/59) after 3 months, 44 % (26/59) after 1 year, and 42 % (25/59) after 2 years of adjunctive VNS. Remission rates were 15 % (9/59) at 3 months, 27 % (16/59) at 1 year, and 22 % (13/59) at 2 years. By 2 years, 2 deaths (unrelated to VNS) had occurred, 4 participants had withdrawn from the study, and 81 % (48/59) were still receiving VNS. Longer-term VNS was generally well-tolerated. These investigators concluded that their findings suggest that patients with chronic or recurrent, TRD may show long-term benefit when treated with VNS.

George et al (2005) stated that previous reports had described the effects of VNS plus treatment as usual (VNS+TAU) during open trials of patients with TRD. To better understand these effects on long-term outcome, these researchers compared 12-month VNS+TAU outcomes with 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 linear regression was used to compare the VNS+TAU group (monthly data) with the TAU group (quarterly data) according to scores of the 30-item Inventory of Depressive Symptomatology-Self-Report (IDS-SR (30)). The 2 groups had similar baseline demographic data, psychiatric and treatment histories, and degrees of treatment resistance, except that more TAU participants had at least 10 prior major depressive episodes, and the VNS+TAU group had more electroconvulsive therapy before study entry. The VNS+TAU group was associated with greater improvement per month in IDS-SR(30) than the TAU group across 12 months (p < 0.001). Response rates according to the 24-item Hamilton Rating Scale for Depression (last observation carried forward) at 12 months were 27 % for the VNS+TAU group and 13 % for the TAU group (p < 0.011). Both groups received similar TAU (drugs and electroconvulsive therapy) during follow-up. These investigators concluded that this comparison of 2 similar but non-randomized TRD groups showed that VNS+TAU was associated with a greater anti-depressant benefit over 12 months. These preliminary findings by Nahas et al (2005) as well as George as et (2005) need to be validated by prospective, randomized placebo-controlled studies.

In a randomized controlled 10-week study, Rush and colleagues (2005a) compared adjunctive VNS with sham treatment in 235 outpatients with non-psychotic major depressive disorder (n = 210) or non-psychotic, depressed phase, bipolar disorder (n = 25). Subjects had not responded adequately to between 2 to 6 research-qualified medication trials. A 2-week, single-blind recovery period (no stimulation) and then 10 weeks of masked active or sham VNS followed implantation. Medications were kept stable. Primary efficacy outcome among 222 evaluable participants was based on response rates (greater than or equal to 50 % reduction from baseline on the 24-item Hamilton Rating Scale for Depression [HRSD(24)]) at 10-weeks, HRSD(24) response rates were 15.2 % for the active (n = 112) and 10.0 % for the sham (n = 110) groups (p = 0.251). Response rates with a secondary outcome, the Inventory of Depressive Symptomatology - Self-Report (IDS-SR(30)), were 17.0 % (active) and 7.3 % (sham) (p = 0.032). Vagal nerve stimulation was well-tolerated; 1 % (3/235) of subjects left the study because of adverse events. These investigators concluded that this study did not yield definitive evidence of short-term effectiveness of adjunctive VNS in TRD.
Rush et al (2005b) described follow-up of outpatients with non-psychotic major depressive (n = 185) or bipolar (I or II) disorder, depressed phase (n = 20) who initially received 10 weeks of active (n = 110) or sham VNS (n = 95). The initial active group received another 9 months, while the initial sham group received 12 months of VNS. Participants received anti-depressant treatments and VNS, both of which could be adjusted. The primary analysis (repeated measures linear regression) revealed a significant reduction in HRSD(24) scores (average improvement, .45 points [SE = .05] per month (p < 0.001). At exit, HRSD(24) response rate was 27.2 % (55/202); remission rate (HRSD(24) less than or equal to 9) was 15.8 % (32/202). Montgomery Asberg Depression Rating Scale (28.2 % [57/202]) and Clinical Global Impression-Improvement (34.0 % [68/200]) showed similar response rates. Voice alteration, dyspnea, and neck pain were the most frequently reported adverse events. These researchers concluded that these 1-year open trial data found VNS to be well-tolerated, suggesting a potential long-term, growing benefit in TRD, albeit in the context of changes in depression treatments. Comparative long-term data are needed to determine whether these benefits can be attributed to VNS.

Furthermore, the BlueCross BlueShield TEC assessment on VNS for TRD (2005) stated that this method does not meet the TEC criteria. The TEC assessment stated that the available evidence is insufficient to permit conclusions of the effect of VNS therapy on health outcomes. According to the TEC assessment, "the available evidence consists of a case series of 60 patients receiving VNS, a short-term (i.e., 3-month) randomized, sham-controlled clinical trial of 221 patients, and an observational study comparing 205 patients on VNS therapy compared to 124 patients receiving ongoing treatment for depression. Patients who responded to sham treatment in the short-term randomized, controlled trial (approximately 10%) were excluded from the long-term observational study. Patient selection was a concern for all studies. VNS is intended for treatment-refractory depression, but the entry criteria of failure of 2 drugs and a 6-week trial of therapy may not be a strict enough definition of treatment resistance. Treatment-refractory depression should be defined by thorough state-of-the-art psychiatric evaluation and management".

The BlueCross BlueShield Association updated their assessment in August 2006, and concluded that VNS does not meet the TEC criteria. The assessment explained that, "[s]ince the last TEC Assessment, there have been no studies reporting clinical outcomes on any new or different patients. Data from the case series and clinical trials have been reanalyzed to show what proportions of patients who respond at one time are still responders at a subsequent time point. However, this information by itself does not provide evidence of the efficacy of VNS beyond that provided by the original observational comparison of VNS versus treatment as usual."

An assessment of VNS for severe depression by the Aggressive Research Intelligence Facility (ARIF, 2005) stated: "To conclude, this is an experimental and as yet unproven method of treatment for severe depression. If this treatment is utilized, patients should be advised of the experimental nature of the treatment and should be assessed by an expert in the field, who is familiar with the treatment. The treatment should ideally be given as part of a robust evaluation of clinical effectiveness and safety in order to add to the current evidence base". Furthermore, an assessment by the California Technology Assessment Forum (CTAF, 2006) concluded that the use of VNS for the treatment of resistant depression does not meet CTAF's technology assessment criteria for safety, effectiveness, and improvement in health outcomes.

George et al (2007) stated that VNS is a new approach in treating neuropsychiatric diseases within the class of brain-stimulating devices known as neuromodulators. Although VNS has received FDA approval for the treatment of medication-resistant depression, there is a lack of Class I evidence of effectiveness in treating depression. The authors concluded that much more research is needed regarding exactly how to refine and deliver the electrical pulses and how this differentially affects brain function in health and disease.

The Centers for Medicare & Medicaid Services (CMS, 2007) stated that there is sufficient evidence to conclude that VNS is not reasonable and necessary for the treatment of resistant
depression. Thus, CMS has announced a national non-coverage determination for this indication.

In a systematic review on the safety and effectiveness of VNS in the management of patients with TRD, Daban and colleagues (2008) concluded that VNS seems to be an interesting new approach to treating TRD. However, despite the promising results reported mainly in open studies, further clinical trials are necessary to confirm its effectiveness in major depression. Moreover, studies on its mechanism of action and cost-effectiveness are also needed to better understand and develop VNS therapy for affective disorder. This is in agreement with the observation of Fitzgerald and Daskalakis (2008) who stated that given the invasive nature of VNS and potential side effects, further research on its use for the treatment of depression is urgently needed. This should include the development of predictors of clinical response and definition of stimulation parameters with enhanced effectiveness.

An Agency for Healthcare Research and Quality's review (Gaynes et al, 2011) reported that there is insufficient evidence to evaluate whether non-pharmacological treatments are effective for TRD. The review summarized evidence of the effectiveness of 4 non-pharmacological treatments: (i) electroconvulsive therapy (ECT), (ii) repetitive transcranial magnetic stimulation (rTMS), (iii) VNS, and (iv) cognitive behavioral therapy (CBT) or interpersonal psychotherapy. With respect to maintaining remission (or preventing relapse), there were no direct comparisons (evidence) involving ECT, rTMS, VNS, or CBT. With regard to indirect evidence, there were 3 fair trials compared rTMS with a sham procedure and found no significant differences, however, too few patients were followed during the relapse prevention phases in 2 of the 3 studies (20-week and 6-month follow-up) and patients in the 3rd study (3-month follow-up) received a co-intervention providing insufficient evidence for a conclusion. There were no eligible studies for ECT, VNS, or psychotherapy.

The review concluded that that comparative clinical research on non-pharmacologic interventions in a TRD population is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS. However, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for benefits, reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change our confidence in these findings. This finding of low strength is most notable in 2 cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for non-pharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between non-pharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing non-pharmacologic interventions with themselves and with pharmacologic treatments, and to delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.

Recently, VNS has been used to treat patients with autism, obesity, Alzheimer’s disease, and obsessive-compulsive disorder. Results from pilot studies suggested that VNS might induce weight loss in obese individuals and improve cognitive function in patients with Alzheimer’s disease. However, these findings need to be validated in large randomized placebo-controlled studies with long-term outcomes.

In an open-label study, Camilleri and associates (2008) evaluated the effects of vagal blocking by means of a new medical device that uses high-frequency electrical algorithms to create intermittent vagal blocking (VBLOC therapy) on excess weight loss (EWL). Electrodes were implanted laparoscopically on both vagi near the esophago-gastric junction to provide electrical block. Patients (obese subjects with body mass index [BMI] of 35 to 50 kg/m(2)) were followed for 6 months for body weight, safety, electrocardiogram, dietary intake, satiation, satiety, and plasma pancreatic polypeptide (PP) response to sham feeding. To specifically assess device
effects alone, no diet or exercise programs were instituted. A total of 31 patients (mean BMI, 41.2 +/- 1.4 kg/m(2)) received the device. Mean EWL at 4 and 12 weeks and 6 months after implant was 7.5 %, 11.6 %, and 14.2 %, respectively (all p < 0.001); 25 % of patients lost over 25 % EWL at 6 months (maximum, 36.8 %). There were no deaths or device-related serious adverse events (AEs). Calorie intake decreased by greater than 30 % at 4 and 12 weeks and 6 months (all p < or = 0.01), with earlier satiation (p < 0.001) and reduced hunger (p = 0.005). After 12 weeks, plasma PP responses were suppressed (20 +/- 7 versus 42 +/- 19 pg/ml). Average percent EWL in patients with PP response less than 25 pg/ml was double that with PP response greater than 25 pg/ml (p = 0.02). Three patients had serious AEs that required brief hospitalization, 1 each for lower respiratory tract, subcutaneous implant site seroma, and clostridium difficile diarrhea. The authors concluded that VBLOC therapy is associated with significant EWL and a desirable safety profile. They noted that these findings have resulted in the design and implementation of a randomized, double-blind, prospective, multi-center trial in an obese subject population.

Vagal nerve stimulation is also being studied for treating chronic headaches; however, its value for this indication has yet to be established. Mauskop (2005) reported that VNS was implanted in 4 men and 2 women with disabling chronic cluster and migraine headaches. In 1 man and 1 woman with chronic migraines, VNS produced dramatic improvement with restoration of ability to work. Two patients with chronic cluster headaches had significant improvement of their headaches. Treatment was well-tolerated in 5 patients, while 1 developed nausea even at the lowest current strength. The author concluded that VNS may be an effective therapy for intractable chronic migraine and cluster headaches and deserves further trials.

Ansari et al (2007) noted that a possible role of VNS in the treatment of severe refractory headache, intractable chronic migraine and cluster headache has been suggested. Clinical trials are ongoing to examine VNS as a potential treatment for essential tremor, cognitive deficits in Alzheimer's disease, anxiety disorders, and bulimia. Furthermore, VNS has also been studied in the treatment of resistant obesity, addictions, sleep disorders, narcolepsy, coma, as well as memory and learning deficits.

In a review on current and future treatments for chronic migraine, Mathew (2009) stated that larger and more accurate studies are needed to further evaluate the usefulness of VNS as a preventive migraine treatment.

In a pilot study, Schwartz et al (2008) examined the feasibility and safety and tested possible efficacy of chronic VNS in patients with heart failure (HF). A total of 8 patients (mean age of 54 years) were included in this study. CardioFit (BioControl Medical), a vagal stimulation implantable system delivering pulses synchronous with heart beats through a multiple contact bipolar cuff electrode, was used. Vagus nerve stimulation was started 2 to 4 weeks after implant, slowly raising intensity; patients were followed 1, 3 and 6 months thereafter. All procedures were successful: as sole surgical side effect, 1 patient had transient hoarseness. Vagal stimulation was well-tolerated, with only mild side effects (cough and sensation of electrical stimulation). There was a significant improvement in NYHA class, Minnesota quality of life (from 52 +/- 14 to 31 +/- 18, p < 0.001), left ventricular end-systolic volume (from 208 +/- 71 to 190 +/- 83 ml, p = 0.03), and a favorable trend toward reduction in end-diastolic volume. The authors concluded that this novel approach in treating patients with HF is feasible, and appears safe and tolerable. They stated that the preliminary efficacy results appear promising, and that these findings suggest the opportunity to proceed with a larger multi-center study.

Rosenberg et al (2009) stated that treatment of mood disorders is one of the most challenging territories in the elderly. Effectiveness of different treatment strategies could be related to age, sex and physical conditions. The side effect profile in this population also affects pharmacological interventions. These investigators reviewed the neurostimulative treatment strategies in this population of patients. However, possible treatment strategies such as electroconvulsive therapy, transcranial magnetic stimulation (TMS), VNS and deep brain stimulation (DBS) were less studied in the elderly. Electroconvulsive therapy was found to be an effective treatment procedure in mood disorders. Few double-blind sham controlled studies were
conducted and demonstrated effectiveness of TMS; and DBS has lack of double-blind studies. Electroconvulsive therapy appears to be the golden standard for the treatment resistant elderly patients despite its side effects. The authors stated that double-blind, sham, controlled studies with larger samples are needed to confirm preliminary results with transcranial direct current stimulation, magnetic seizure therapy, DBS as well as VNS.

Jaseja (2008) stated that cerebral palsy (CP) continues to pose a cause for major socio-economic concern and medical challenge worldwide. It is associated with a multi-faceted symptomatology warranting a multi-dimensional management-approach. Recent recognition of neurocognitive impairment and its hopefully possible treatment has opened up a new dimension in its management to the neurologists. Vagal nerve stimulation technique is presently emerging as an effective alternative anti-epileptic therapeutic measure in intractable epilepsy. Vagus nerve stimulation has recently been shown to possess a suppressive effect also on interictal epileptiform discharges (IEDs) that are now being widely accepted as established associates of neurocognitive impairment. The author proposed VNS technique implantation in CP patients on account of its dual therapeutic effectiveness, i.e., anti-epileptic and IED-suppression. These 2 effects are likely to control seizures that are quite often drug-resistant and also improve neurocognition in CP patients, thus hoping for a better overall prognostic outcome and an improved quality of life of the CP patients by VNS.

Kraus et al (2007) stated that direct VNS has proved to be an effective treatment for seizure disorder. However, since this invasive technique implies surgery, with its side-effects and relatively high financial costs, a non-invasive method to stimulate vagal afferences would be a great step forward. These researchers studied effects of non-invasive electrical stimulation of the nerves in the left outer auditory canal in healthy subjects (n = 22), aiming to activate vagal afferences transcutaneously (tVNS). Short-term changes in brain activation and subjective well-being induced by tVNS were investigated by functional magnetic resonance imaging (fMRI) and psychometric assessment using the adjective mood scale (AMS), a self-rating scale for current subjective feeling. Stimulation of the ear lobe served as a sham control. Functional MRI showed that robust tVNS induced blood oxygenation level dependent (BOLD)-signal decreases in limbic brain areas, including the amygdala, hippocampus, para-hippocampal gyrus and the middle and superior temporal gyrus. Increased activation was seen in the insula, precentral gyrus and the thalamus. Psychometric assessment revealed significant improvement of well-being after tVNS. Ear lobe stimulation as a sham control intervention did not show similar effects in either fMRI or psychometric assessment. No significant effects on heart rate, blood pressure or peripheral microcirculation could be detected during the stimulation procedure. The authors concluded that these findings showed the feasibility and beneficial effects of tVNS in the left auditory canal of healthy subjects.

Dietrich and colleagues (2008) stated that left cervical VNS using the implanted NCP can reduce epileptic seizures. To address a disadvantage of this device, the use of an alternative transcutaneous electrical nerve stimulation technique, designed for muscular stimulation, was studied. Functional MRI has been used to test non-invasively access nerve structures associated with the vagus nerve system. The results and their impact were unsatisfying due to missing brainstem activations. These activations, however, are mandatory for reasoning, higher subcortical and cortical activations of vagus nerve structures. The objective of this study was to test a new parameter setting and a novel device for performing specific tVNS at the inner side of the tragus. This study showed the feasibility of these and their potential for brainstem and cerebral activations as measured by BOLD fMRI. In total, 4 healthy male adults were scanned inside a 1.5-Tesla MR scanner while undergoing tVNS at the left tragus. These investigators ensured that their newly developed tVNS stimulator was adapted to be an MRI-safe stimulation device. In the experiment, cortical and brainstem representations during tVNS were compared to a baseline. A positive BOLD response was detected during stimulation in brain areas associated with higher order relay nuclei of vagal afferent pathways, the left locus coeruleus, the thalamus, the left prefrontal cortex, the right and the left postcentral gyrus, the left posterior cingulated gyrus and the left insula, respectively. Deactivations were found in the right nucleus accumbens...
and the right cerebellar hemisphere. The authors concluded that this method and device are feasible and appropriate for accessing cerebral vagus nerve structures.

Xiong et al (2009) stated that post-operative cognitive dysfunction (POCD) is a decline in cognitive function for weeks or months after surgery. It may affect the patients’ length of hospital stay, quality of life, the rehabilitation process, and work performance. Prolonged POCD occurs frequently after cardiac surgery, and the risk of POCD increases with age. The pathophysiology of POCD is not well-understood. However, emerging evidences indicate that various inflammatory mediators are involved in the pathophysiology of POCD and inflammatory response may be a potential pathogenic factor. Vagus nerve stimulation has been shown to decrease production and release of pro-inflammatory cytokines through the cholinergic anti-inflammatory pathway (CAP) in both animal model and human. Considering that inflammation plays a definite role in the pathogenesis of POCD and the vagus nerve can mediate inflammation via CAP, these researchers hypothesized that transcutaneous VNS may attenuate POCD by reducing inflammatory response in elderly patients.

Hemicrania continua is a rare, relentless, constant, 1-sided headache that is accompanied at times by mild symptoms related to dysfunction of the autonomic nervous system in the face -- small pupil, drooping eyelid, red or watering eye, stuffy or runny nose -- similar to the symptoms of a cluster headache, but much less dramatic. The pain is usually dull but can wax and wane in severity. These headaches often subside entirely with prescription anti-inflammatory medication.

Magis et al (2011) stated that cluster headache is well known as one of the most painful primary neurovascular headache. Since 1% of chronic cluster headache patients become refractory to all existing pharmacological treatments, various invasive and sometimes mutilating procedures have been tried in the last decades. Recently, neurostimulational approaches have raised new hope for drug-resistant chronic cluster headache patients. The authors reviewed the evidence on stimulation of the great occipital nerve, which has been the best evaluated peripheral nerve stimulation technique in drug-resistant chronic cluster headache, providing the most convincing results so far. Other peripheral nerve stimulation approaches used for this indication were also reviewed in detail. They noted that "[a]lthough available studies are limited to a relatively small number of patients and placebo-controlled trials are lacking .... More studies are needed to evaluate the usefulness of supraorbital nerve stimulation and of vagus nerve stimulation in management of cluster headaches".

Martin and Martin-Sanchez (2012) evaluated the effectiveness of VNS for treatment of depression. These researchers conducted a systematic review and meta-analysis of analytical studies. Effectiveness was evaluated according to severity of illness and percentage of responders. They identified 687 references. Of these, 14 met the selection criteria and were included in the review. The meta-analysis of effectiveness 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% to 41.8%], p < 0.001). However, the randomized controlled trial that covered a sample of 235 patients with depression, reported no statistically significant differences between the active intervention and placebo groups (odds ratio [OR] = 1.61 [95% confidence interval [CI]: 0.72 to 3.62]; p = 0.25). To study the cause of this heterogeneity, a meta-regression was performed. The adjusted co-efficient of determination (R2 (Adj)) was 0.84, which implies that an 84% variation in effect size across the studies was explained by baseline severity of depression (p < 0.0001). The authors concluded that currently, insufficient data are available to describe VNS as effective in the treatment of depression. In addition, it cannot be ruled out that the positive results observed in the uncontrolled studies might have been mainly due to a placebo effect.

In a pilot study, Lehtimaki et al (2013) examined if transcutaneous VNS (tVNS) combined with sound therapy (ST) would reduce the severity of tinnitus and tinnitus-associated distress. The objectives were to study whether tVNS has therapeutic effects on patients with tinnitus and, additionally, if tVNS has effects on acoustically evoked neuronal activity of the auditory cortex. The clinical efficacy was studied by a short-term tVNS plus ST trial in 10 patients with tinnitus using disease-specific and general well-being questionnaires. Transcutaneous VNS was
delivered to the left tragus. The acute effects of tVNS were evaluated in 8 patients in the MEG study in which the N1m response was analyzed in terms of source level amplitude and latency in the presence or absence of tVNS. The treatment with tVNS plus ST produced improved mood and decreased tinnitus handicap scores, indicating reduced tinnitus severity. The application of tVNS decreased the amplitude of auditory N1m responses in both hemispheres. The results of this pilot study need to be validated by well-designed studies.

Straube et al (2012) stated that chronic migraine (CM) was first defined in the second edition of the International Headache Society (IHS) classification in 2004. The definition currently used (IHS 2006) requires the patient to have headache on more than 15 days/month for longer than 3 months and a migraine headache on at least 8 of these monthly headache days and that there is no medication overuse. In daily practice the majority of the patients with CM also report medication overuse but it is difficult to determine whether the use is the cause or the consequence of CM. Most the patients also have other co-morbidities, such as depression, anxiety and chronic pain at other locations. Therapy has to take this complexity into consideration and is generally multi-modal with behavioral therapy, aerobic training and pharmacotherapy. The use of analgesics should be limited to fewer than 15 days per month and use of triptans to fewer than 10 days per month. Drug treatment should be started with topiramate, the drug with the best scientific evidence. If there is no benefit, onabotulinum toxin A (155 to 195 Units) should be used. There is also some limited evidence that valproic acid and amitriptyline might be beneficial. Moreover, the authors stated that neuromodulation by stimulation of the greater occipital nerve or vagal nerve is being tested in studies and is so far an experimental procedure only.

On behalf of the Guideline Development Subcommittee of the American Academy of Neurology (AAN), Morris et al (2013) evaluated the evidence since the 1999 assessment regarding safety and effectiveness of (VNS for epilepsy, currently approved as adjunctive therapy for partial-onset seizures in patients greater than 12 years of age. These investigators reviewed the literature and identified relevant published studies. They classified these studies according to the AAN evidence-based methodology. Vagal nerve stimulation is associated with a greater than 50 % seizure reduction in 55 % (95 % CI: 50 % to 59 %) of 470 children with partial or generalized epilepsy (13 Class III studies). Vagal nerve stimulation is associated with a greater than 50 % seizure reduction in 55 % (95 % CI: 46 % to 64 %) of 113 patients with Lennox-Gastaut syndrome (LGS) (4 Class III studies). Vagal nerve stimulation is associated with an increase in greater than or equal to 50% seizure frequency reduction rates of approximately 7 % from 1 to 5 years post-implantation (2 Class III studies). Vagal nerve stimulation is associated with a significant improvement in standard mood scales in 31 adults with epilepsy (2 Class III studies). Infection risk at the VNS implantation site in children is increased relative to that in adults (OR = 3.4, 95 % CI: 1.0 to 11.2). Vagal nerve stimulation is possibly effective for seizures (both partial and generalized) in children, for LGS-associated seizures, and for mood problems in adults with epilepsy; it may have improved efficacy over time. The authors concluded that VNS may be considered for seizures in children, for LGS-associated seizures, and for improving mood in adults with epilepsy (Level C); it may be considered to have improved efficacy over time (Level C). Children should be carefully monitored for site infection after VNS implantation. Moreover, these researchers noted that some reports have discussed VNS use in small numbers of patients with juvenile myoclonic epilepsy (JME); they stated that larger reports would help substantiate whether VNS is appropriate in medically refractory JME.

McClelland et al (2013) stated that eating disorders (ED) are chronic and sometimes deadly illnesses. Existing treatments have limited proven efficacy, especially in the case of adults with anorexia nervosa. Emerging neural models of ED provide a rationale for more targeted, brain-directed interventions. In a systematic review, these investigators examined the effects of neuromodulation techniques on eating behaviors and body weight and assessed their potential for therapeutic use in ED. All articles in PubMed, PsychInfo and Web of Knowledge were considered and screened against a priori inclusion/exclusion criteria. The effects of repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation, VNS and deep brain stimulation (DBS) were examined across studies in ED samples, other psychiatric and
neurological disorders, and animal models. A total of 60 studies were identified. There is evidence for ED symptom reduction following rTMS and DBS in both anorexia nervosa and bulimia nervosa. Findings from studies of other psychiatric and neurological disorders and from animal studies demonstrated that increases in food intake and body weight can be achieved following DBS and that VNS has potential value as a means of controlling eating and inducing weight loss. The authors concluded that neuromodulatory tools have potential for reducing ED symptomatology and related behaviors, and for altering food intake and body weight. They stated that more research is needed to evaluate the potential of neuromodulatory procedures for improving long-term outcomes in ED.

Elliott et al (2011a) evaluated the safety and effectiveness of VNS in a consecutive series of adults and children with treatment-resistant epilepsy (TRE). In this retrospective review of a prospectively created database of 436 consecutive patients who underwent VNS implantation for TRE between November 1997 and April 2008, there were 220 (50.5 %) females and 216 (49.5 %) males ranging in age from 1 to 76 years at the time of implantation (mean of 29.0 ± 16.5). Thirty-three patients (7.6 %) in the primary implantation group had inadequate follow-up (less than 3 months from implantation) and 3 patients had early device removal because of infection and were excluded from seizure control outcome analyses. Duration of VNS treatment varied from 10 days to 11 years (mean of 4.94 years). Mean seizure frequency significantly improved following implantation (mean reduction of 55.8 %, p < 0.0001). Seizure control greater than or equal to 90 % was achieved in 90 patients (22.5 %), greater than or equal to 75 % seizure control in 162 patients (40.5 %), greater than or equal to 50 % improvement in 255 patients (63.75 %), and less than 50 % of patients. The authors concluded that VNS is a safe and effective palliative treatment option for focal and generalized TRE in adults and children. When used in conjunction with a multi-disciplinary and multi-modality treatment regimen including aggressive anti-epileptic drug regimens and epilepsy surgery when appropriate, more than 60 % of patients with TRE experienced at least a 50 % reduction in seizure burden. Good results were seen in patients with non FDA-approved indications. Moreover, they stated that prospective, randomized trials are needed for patients with generalized epilepsies and for younger children to potentially expand the number of patients who may benefit from this palliative treatment. The authors also noted the following drawbacks of the study: (i) although patients were entered prospectively into the database, this study was performed via retrospective query. Follow-up was unavailable in 8 % of patients, providing a small margin of error in the estimates of VNS efficacy. Determination of seizure frequency and use and efficacy of magnetic swiping relied on the report of patients or caretakers and is inherently subject to error, (ii) a design limitation inherent to all retrospective, non-randomized studies on VNS is the lack of a control group, and (iii) a potential confound is the effect of AED (anti-epileptic drug) regimen changes on seizure frequency over time in the setting of VNS. Many office visits were accompanied by VNS setting changes and, much more frequently, by AED regimen adjustments (medication and/or dosage changes). The complexity and frequency of such changes (often multiple changes in a single visit) proved too difficult to incorporate into a meaningful analysis. The authors could not control for all of these changes but believe AED treatment plays a major role in the success of any treatment plan that includes long-term VNS therapy. In fact, the increase in VNS efficacy over time reported by numerous centers may be due to alteration in device parameters, changes in AED regimen, or an undefined, synergistic effect of both.

Elliott et al (2011b) analyzed the effectiveness of VNS in a large consecutive series of children 18 years of age and younger with TRE and compared the safety and effectiveness in children under 12 years of age with the outcomes in older children. These researchers retrospectively reviewed 141 consecutive cases involving children (75 girls and 66 boys) with TRE in whom primary VNS implantation was performed by the senior author between November 1997 and April 2008 and who had at least 1 year of follow-up since implantation. The patients' mean age at VNS insertion was 11.1 years (range of 1 to 18 years). Eighty-six children (61.0 %) were younger than 12 years at time of VNS insertion (which constitutes off-label usage of this device). Follow-up was complete for 91.8 % of patients and the mean duration of VNS therapy in these patients was 5.2 years (range of 25 days to 11.4 years). Seizure frequency significantly
improved with VNS therapy (mean reduction of 58.9 %, p < 0.0001) without a significant reduction in anti-epileptic medication burden (median number of anti-epileptic drugs taken 3, unchanged). Reduction in seizure frequency of at least 50 % occurred in 64.8 % of patients and 41.4 % of patients experienced at least a 75 % reduction. Major (3) and minor (6) complications occurred in 9 patients (6.4 %) and included 1 deep infection requiring device removal, 1 pneumothorax, 2 superficial infections treated with antibiotics, 1 seroma/hematoma treated with aspiration, persistent cough in 1 patient, severe but transient neck pain in 1 patient, and hoarseness in 2 patients. There was no difference in efficacy or complications between children 12 years of age and older (FDA-approved indication) and those younger than 12 years of age (off-label usage). Linear regression analyses did not identify any demographic and clinical variables that predicted response to VNS. The authors concluded that VNS is a safe and effective treatment for TRE in young adults and children. Over 50 % of patients experienced at least 50 % reduction in seizure burden. Children younger than 12 years had a response similar to that of older children with no increase in complications. Moreover, they stated that given the efficacy of this device and the devastating effects of persistent epilepsy during critical developmental epochs, randomized trials are needed to potentially expand the indications for VNS to include younger children. Moreover, the authors stated that this study was limited by the retrospective query into a prospective database and was subject to biases inherent to such methodology. Nearly 8 % of patients were unavailable for follow-up. Determination of seizure frequency relied on the reports of patients or caretakers and is inherently subject to error and bias. This limitation is common to many studies measuring seizure frequency and treatment outcomes. These researchers tried to improve their estimates by using LVCF (last value carried forward) analysis instead of declining-n analysis, which is prone to non-responder attrition. Detailed information on the effects of VNS on mood, quality of life, and qualitative aspects of seizures (duration, severity, clustering, postictal period, and magnet usage) were either not systematically reported or could not be derived from this retrospective analysis. Moreover, these investigators did not determine if a mean reduction in seizures of nearly 50 % translates into caretaker and patient satisfaction and overall improvements in quality of life. They stated that future prospective studies are needed to better ascertain baseline mood assessments, quality-of-life metrics, and caretaker satisfaction and to determine the impact of VNS on these parameters and their relation to seizure control. Another confound concerns the unknown impact that changes in AED regimens have on seizure frequency over time in the setting of VNS. Many office visits were accompanied by VNS setting changes and, more frequently, by AED regimen adjustments. The authors could not control for these changes but believe AED treatment plays a major role in the success of any treatment plan, including long-term VNS therapy. They stated that further study is needed to better understand the relative contributions of effective VNS therapy, AED regimen adjustments, and regression to the mean.

The study by Elliott et al (2011b) (effects of VNS on children) appeared to be a sub-analysis of the study by Elliott et al 2011a (effects of VNS on adults and children).

An UpToDate review on “Vagus nerve stimulation therapy for the treatment of epilepsy” (Karceski and Schachter, 2014) states that “The Food and Drug Administration (FDA) has approved vagus nerve stimulator (VNS) therapy as adjunctive treatment for adults and adolescents over 12 years of age whose partial-onset seizures were refractory to antiepileptic drugs. Since the approval of VNS therapy for epilepsy, clinicians have actively debated its role. While further controlled studies are needed to more fully understand the safety, tolerability, and efficacy profile of VNS in children and in patients with generalized seizures, VNS is often used in these cases as well ….

Case series suggest that VNS is also effective in generalized epilepsy syndromes. While some studies found that symptomatic generalized epilepsy is more responsive to VNS than idiopathic syndromes, others have reported the opposite or found no difference”.

Huang et al (2014) noted that impaired glucose tolerance (IGT) is a pre-diabetic state of hyperglycemia that is associated with insulin resistance, increased risk of type II diabetes, and cardiovascular pathology. Recently, investigators hypothesized that decreased vagus nerve activity may be the underlying mechanism of metabolic syndrome including obesity, elevated glucose levels, and high blood pressure (BP). In this pilot randomized clinical trial (RCT), these
researchers compared the effectiveness of transcutaneous auricular VNS (taVNS) and sham-taVNS on patients with IGT. A total of 72 participants with IGT were single-blinded and were randomly allocated by computer-generated envelope to either taVNS or sham-taVNS treatment groups. In addition, 30 IGT adults were recruited as a control population and not assigned treatment so as to monitor the natural fluctuation of glucose tolerance in IGT patients. All treatments were self-administered by the patients at home after training at the hospital. Patients were instructed to fill in a patient diary booklet each day to describe any side effects after each treatment. The treatment period was 12 weeks in duration. Baseline comparison between treatment and control group showed no difference in weight, BMI, or measures of systolic BP, diastolic BP, fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), or glycosylated hemoglobin (HbA1c). A total of 100 participants completed the study and were included in data analysis. Two female patients (1 in the taVNS group, 1 in the sham-taVNS group) dropped out of the study due to stimulation-evoked dizziness. The symptoms were relieved after stopping treatment. Compared with sham-taVNS, taVNS significantly reduced the 2-hour glucose tolerance (F(2) = 5.79, p = 0.004). In addition, these investigators found that taVNS significantly decreased (F(1) = 4.21, p = 0.044) systolic BP over time compared with sham-taVNS. Compared with the no-treatment control group, patients receiving taVNS significantly differed in measures of FPG (F(2) = 10.62, p < 0.001), 2hPG (F(2) = 25.18, p < 0.001) and HbA1c (F(1) = 12.79, p = 0.001) over the course of the 12-week treatment period. The authors concluded that the findings of this study suggested that taVNS is a promising, simple, and cost-effective treatment for IGT/ pre-diabetes with only slight risk of mild side-effects.

Cai et al (2014) stated that because of its ability to regulate mechanisms well-studied in neuroscience, such as norepinephrine and serotonin release, the vagus nerve may play an important role in regulating cerebral blood flow, edema, inflammation, glutamate excitotoxicity, and neurotrophic processes. There is strong evidence that these same processes are important in stroke pathophysiology. These investigators reviewed the literature for the role of VNS in improving ischemic stroke outcomes by performing a systematic search for publications in Medline (1966 to 2014) with keywords "VNS AND stroke" in subject headings and key words with no language restrictions. Of the 73 publications retrieved, these researchers identified 7 studies from 3 different research groups that met the final inclusion criteria of research studies addressing the role of VNS in ischemic stroke. Results from these studies suggested that VNS has promising efficacy in reducing stroke volume and attenuating neurological deficits in ischemic stroke models. Given the lack of success in phase III trials for stroke neuroprotection, it is important to develop new therapies targeting different neuroprotective pathways. The authors concluded that further studies of the possible role of VNS, through normally physiologically active mechanisms, in ischemic stroke therapeutics should be conducted in both animal models and clinical studies. In addition, recent advent of a non-invasive, transcutaneous VNS could provide the potential for easier clinical translation.

Hall et al (2014) stated that nosocomial infections, pneumonia in particular, are well-known complications of traumatic brain injury (TBI), which are associated with a worse neurological outcome. These researchers explored the role of vagus nerve activity in immunomodulation as a causative factor. A MEDLINE search revealed numerous reports published over the last decade describing the "cholinergic anti-inflammatory pathway" between the vagus nucleus and leukocyte activity. Using a combination of lipopolysaccharide stimulation and vagotomy, it has been shown that the parasympathetic fibers terminating in the spleen reduce tumor necrosis factor (TNF) production. Further pharmacological and receptor knockout studies have identified the α7 subtype of nicotinic receptors as the likely target for this. Vagal activity also induces changes in neutrophil chemotaxis through altered expression of the CD11b integrin which is abolished by splenectomy. By extrapolating this evidence these investigators suggested a possible mechanism for immunosuppression following TBI, which also has the potential to be targeted to reduce the incidence of pneumonia. The authors concluded that while there is strong supporting evidence for the role of vagal nerve over-activity in post-TBI pneumonia, there have yet to be any clinical investigations and further study is needed.
Zhou et al (2014) noted that previous studies have shown that VNS can improve the prognosis of TBI. These researchers examined the mechanism of the neuroprotective effects of VNS in rabbits with brain explosive injury. Rabbits with brain explosive injury received continuous stimulation (10 V, 5 Hz, 5 ms, 20 minutes) of the right cervical vagus nerve. Tumor necrosis factor-α, interleukin (IL)-1β and IL-10 concentrations were detected in serum and brain tissues, and water content in brain tissues was measured. Results showed that VNS could reduce the degree of brain edema, decrease TNF-α and IL-1β concentrations, and increase IL-10 concentration after brain explosive injury in rabbits. The authors concluded that these data suggested that VNS may exert neuroprotective effects against explosive injury via regulating the expression of TNF-α, IL-1β and IL-10 in the serum and brain tissue.

Howland (2014) noted that right cervical VNS is effective for treating heart failure in pre-clinical studies and a phase II clinical trial. The effectiveness of various forms of non-invasive transcutaneous VNS for epilepsy, depression, primary headaches, and other conditions has not been investigated beyond small pilot studies. The relationship between depression, inflammation, metabolic syndrome, and heart disease might be mediated by the vagus nerve. The author concluded that VNS deserves further study for its potentially favorable effects on cardiovascular, cerebrovascular, metabolic, and other physiological biomarkers associated with depression morbidity and mortality.

Appendix

Exclusion Criteria for VNS Therapy of Partial Onset Seizures:

- VNS can not be used in persons with left or bilateral cervical vagotomy
- VNS is not indicated for persons with other types of seizures.

CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61885</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array</td>
</tr>
<tr>
<td>64553</td>
<td>Percutaneous implantation of neurostimulator electrode array; cranial nerve</td>
</tr>
<tr>
<td>64568</td>
<td>Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator</td>
</tr>
<tr>
<td>64569</td>
<td>Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator</td>
</tr>
<tr>
<td>64570</td>
<td>Removal of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator</td>
</tr>
<tr>
<td>95970</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (i.e., cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming</td>
</tr>
</tbody>
</table>
95974  complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour
+ 95975  complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, each additional 30 minutes after first hour (List separately in addition to code for primary procedure)

**CPT codes not covered for indications listed in the CPB:**

0312T  Vagus nerve blocking therapy (morbid obesity); laparoscopic implantation of neurostimulator electrode array, anterior and posterior vagal trunks adjacent to esophagogastric junction (EGJ), with implantation of pulse generator, includes programming

0313T  Vagus nerve blocking therapy (morbid obesity); laparoscopic revision or replacement of vagal trunk neurostimulator electrode array, including connection to existing pulse generator

0317T  Vagus nerve blocking therapy (morbid obesity); neurostimulator pulse generator electronic analysis, includes reprogramming when performed

64550  Application of surface (transcutaneous) neurostimulator [not covered for transcutaneous vagus nerve stimulation]

**Other CPT codes related to the CPB:**

0314T  Vagus nerve blocking therapy (morbid obesity); laparoscopic removal of vagal trunk neurostimulator electrode array and pulse generator

0315T  Vagus nerve blocking therapy (morbid obesity); removal of pulse generator

0316T  Vagus nerve blocking therapy (morbid obesity); replacement of pulse generator

**HCPCS codes covered if selection criteria are met:**

C1767  Generator, neurostimulator (implantable), nonrechargeable

C1778  Lead, neurostimulator (implantable)

C1816  Receiver and/or transmitter, neurostimulator (implantable)

C1883  Adaptor/extension, pacing lead or neurostimulator lead (implantable)

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

L8689  External recharging system for battery (internal) for use with implanted neurostimulator, replacement only

L8695  External recharging system for battery (external) for use with implantable neurostimulator, replacement only

ICD-9 codes covered if selection criteria are met:

345.40 - 345.41  Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures [not covered for transcutaneous vagus nerve stimulation]

345.50 - 345.51  Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures [not covered for transcutaneous vagus nerve stimulation]

ICD-9 codes not covered for indications listed in the CPB:

278.00 - 278.01  Obesity
291.82  Alcohol-induced sleep disorders
292.85  Drug-induced sleep disorders
296.00 - 296.99  Episodic mood disorders
298.0  Depressive type psychosis
299.00 - 299.01  Autistic disorder
300.00 - 300.09  Anxiety states
300.3  Obsessive-compulsive disorders
300.4  Dysthymic disorder
301.11  Chronic hypomanic personality disorder
303.00 - 303.93  Alcohol dependence syndrome
304.00 - 304.93  Drug dependence
305.00 - 305.93  Nondependent abuse of drugs
307.1  Anorexia nervosa
307.23  Tourette's disorder
307.40 - 307.49  Specific disorders of sleep of nonorganic origin
307.50 - 307.59  Other and unspecified disorders of eating
307.81  Tension headache
311  Depressive disorder, not elsewhere classified
327.19  Other organic hypersomnias
327.30 - 327.39 Circadian rhythm sleep disorder
327.40 - 327.49 Organic parasomnia
327.51 - 327.59 Organic sleep related movement disorders
327.8 Other organic sleep disorders
331.0 Alzheimer's disease
333.1 Essential and other specified forms of tremor
339.10 Tension type headache, unspecified
339.41 Hemicrania continua
343.0 - 343.9 Infantile cerebral palsy
345.00 - 345.3 Epilepsy [other than partial onset]
345.60 - 345.91 Epilepsy [other than partial onset]
346.00 - 346.93 Migraine
347.00 - 347.11 Cataplexy and narcolepsy
388.30 - 388.32 Tinnitus
398.91 Rheumatic heart failure (congestive)
402.01 Hypertensive heart disease, malignant, with heart failure
402.11 Hypertensive heart disease, benign, with heart failure
402.91 Hypertensive heart disease, unspecified, with heart failure
404.01 Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.03 Hypertensive heart and chronic kidney disease, malignant, with heart failure and chronic kidney disease stage V or end stage renal disease
404.11 Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13 Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91 Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93 Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
428.0 - 428.9 Heart failure
729.1 Myalgia and myositis, unspecified [fibromyalgia]
780.01 Coma
780.39 Other convulsions [seizure NOS]
780.50 - 780.59  Sleep disturbances
783.6  Polyphagia
784.0  Headache

The above policy is based on the following references:


76. Straube A, Gaul C, Forderreuther S, et al; German Migraine and Headache Society; German Society for Neurology; Austrian Headache Society; Swiss Headache Society. Therapy and care of patients with chronic migraine: Expert recommendations of the German Migraine and Headache Society/German Society for Neurology as well as the...


