VAGUS NERVE STIMULATION

Policy Number: SURGERY 073.12 T2
Effective Date: December 1, 2015

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONDITIONS OF COVERAGE</td>
<td>1</td>
</tr>
<tr>
<td>BENEFIT CONSIDERATIONS</td>
<td>2</td>
</tr>
<tr>
<td>COVERAGE RATIONALE</td>
<td>2</td>
</tr>
<tr>
<td>APPLICABLE CODES</td>
<td>3</td>
</tr>
<tr>
<td>DESCRIPTION OF SERVICES</td>
<td>4</td>
</tr>
<tr>
<td>CLINICAL EVIDENCE</td>
<td>4</td>
</tr>
<tr>
<td>U.S. FOOD AND DRUG ADMINISTRATION</td>
<td>11</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>12</td>
</tr>
<tr>
<td>POLICY HISTORY/REVISION INFORMATION</td>
<td>15</td>
</tr>
</tbody>
</table>

The services described in Oxford policies are subject to the terms, conditions and limitations of the Member’s contract or certificate. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage enrollees. Oxford reserves the right, in its sole discretion, to modify policies as necessary without prior written notice unless otherwise required by Oxford’s administrative procedures or applicable state law. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

Certain policies may not be applicable to Self-Funded Members and certain insured products. Refer to the Member’s plan of benefits or Certificate of Coverage to determine whether coverage is provided or if there are any exclusions or benefit limitations applicable to any of these policies. If there is a difference between any policy and the Member’s plan of benefits or Certificate of Coverage, the plan of benefits or Certificate of Coverage will govern.

CONDITIONS OF COVERAGE

<table>
<thead>
<tr>
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<th>This policy applies to Oxford Commercial plan membership.</th>
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<tr>
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<td>General benefits package</td>
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<tr>
<td>Referral Required</td>
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<td>(Does not apply to non-gatekeeper products)</td>
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<tr>
<td>Authorization Required</td>
<td>Yes¹</td>
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<tr>
<td>(Precertification always required for inpatient admission)</td>
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<tr>
<td>Precertification with Medical Director Review Required</td>
<td>No¹ ²</td>
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<tr>
<td>Applicable Site(s) of Service</td>
<td>Inpatient, Outpatient, Office¹</td>
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<td>(If site of service is not listed, Medical Director review is required)</td>
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<tr>
<td>Special Considerations</td>
<td>¹Electronic analysis of an implanted neurostimulator pulse generator system (CPT codes 95970, 95974 and 95975) does not require Medical Director review in any setting, and requires only a referral when performed in the office setting. ²Medical Director review is required for any diagnosis/indication not listed in the Payment</td>
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</table>
Vagus Nerve Stimulation (VNS) is proven and medically necessary for treating epilepsy in patients with all of the following:

- Medically refractory epileptic seizures
- The patient is not a surgical candidate or has failed a surgical intervention
- No history of left or bilateral cervical vagotomy

The U.S. Food and Drug Administration (FDA) identifies a history of left or bilateral cervical vagotomy as a contraindication to vagus nerve stimulation.

It is an expectation that the physician have experience and expertise in the use of vagus nerve stimulation.

Vagus nerve stimulation is unproven and not medically necessary for treating all other indications, including but not limited to the following:

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

Available studies on the use of vagus nerve stimulation for treating severe, major depression or bipolar disorder refractory to medical therapy contain methodological flaws such as lack of control group, small sample size, potential bias, lack of randomization and blinding and lack of statistical power analysis. There is a substantial placebo effect associated with depression treatments and
the lack of data from prospective randomized controlled or comparative clinical studies considerably limits the conclusions that can be drawn from the available evidence. Furthermore, preliminary analysis of a randomized controlled trial did not find a statistically significant difference between sham and active VNS. Definitive patient selection criteria for vagus nerve stimulation (VNS) in patients with treatment-resistant depression have not yet been established, and significant predictors of response have also not been identified.

Early research has examined the use of vagus nerve stimulation for additional indications. However, because of limited studies, small sample sizes and weak study designs, there is insufficient data to conclude that vagus nerve stimulation is safe and/or effective for treating these indications.

**APPLICABLE CODES**

The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

**Applicable CPT Codes**

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<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
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</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 (e.g., vagus nerve) neurostimulator electrode array and pulse generator</td>
</tr>
<tr>
<td>64570</td>
<td>Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator</td>
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<tr>
<td>95970*</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse 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>
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<tr>
<td>95974*</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour</td>
</tr>
<tr>
<td>95975*</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); 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)</td>
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*CPT® is a registered trademark of the American Medical Association.

*Medical Director review is not required in any setting, and precertification is not required when performed in the office setting.
Applicable HCPCS Codes

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<th>HCPCS Code</th>
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</thead>
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<td>C1767</td>
<td>Generator, neurostimulator (implantable), nonrechargeable</td>
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<tr>
<td>C1778</td>
<td>Lead, neurostimulator (implantable)</td>
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<tr>
<td>L8679</td>
<td>Implantable neurostimulator, pulse generator, any type</td>
</tr>
<tr>
<td>L8680</td>
<td>Implantable neurostimulator electrode (with any number of contact points), each</td>
</tr>
<tr>
<td>L8682</td>
<td>Implantable neurostimulator radiofrequency receiver</td>
</tr>
<tr>
<td>L8683</td>
<td>Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver</td>
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<tr>
<td>L8685</td>
<td>Implantable neurostimulator pulse generator, single array, rechargeable, includes extension</td>
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<td>L8686</td>
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<td>Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension</td>
</tr>
</tbody>
</table>

DESCRIPTION OF SERVICES

The vagus nerve, a large nerve in the neck, connects the lower part of the brain to the heart, lungs and intestines. Vagus nerve stimulation (VNS) uses short bursts of electrical energy directed into the brain via the vagus nerve. The system, implanted subcutaneously in the upper chest, includes a pulse generator/neurostimulator and electrode that deliver pulses of current to the left vagus nerve. Following implantation, the generator is programmed to stimulate the vagus nerve at a rate determined by the patient and physician.

CLINICAL EVIDENCE

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

Englot et al. (2011) performed a meta-analysis of VNS efficacy in epilepsy, identifying 74 clinical studies with 3321 patients suffering from intractable epilepsy. These studies included 3 blinded, randomized controlled trials (Class I evidence); 2 non-blinded, randomized controlled trials (Class II evidence); 10 prospective studies (Class III evidence); and numerous retrospective studies. After VNS, seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures at 3-12 months after surgery and a 51% reduction after > 1 year of therapy. At the last follow-up, seizures were reduced by 50% or more in approximately 50% of the patients. Patients with generalized epilepsy and children benefited significantly from VNS despite their exclusion from initial approval of the device. Furthermore, posttraumatic epilepsy and tuberous sclerosis were positive predictors of a favorable outcome. The authors concluded that VNS is an effective and relatively safe adjunctive therapy in patients with medically refractory epilepsy not amenable to resection. However, the authors commented further that complete seizure freedom is rarely achieved using VNS and that a quarter of patients do not receive any benefit from therapy.
Elliott et al. (2011a) assessed the efficacy and safety of vagus nerve stimulation in a consecutive series of adults and children with treatment-resistant epilepsy (TRE). The study included 220 (50.5%) females and 216 (49.5%) males ranging in age from 1 to 76 years at the time of implantation. Thirty-three patients (7.6%) in the primary implantation group had inadequate follow-up (<3 months from implantation) and three patients had early device removal because of infection and were excluded from seizure control outcome analyses. Mean seizure frequency significantly improved following implantation. Seizure control ≥90% was achieved in 22.5% of patients, ≥75% seizure control in 40.5% of patients, ≥50% improvement in 63.75% of patients, and <50% improvement in 36.25% of patients. Permanent injury to the vagus nerve occurred in 2.8% of patients. The authors concluded that vagus nerve stimulation is a safe and effective palliative treatment option for focal and generalized TRE in adults and children. The authors stated that when used in conjunction with a multidisciplinary and multimodality treatment regimen including aggressive antiepileptic drug regimens and epilepsy surgery when appropriate; more than 60% of patients with TRE experienced at least a 50% reduction in seizure burden.

Elliott et al. (2011b) evaluated the impact of failed intracranial epilepsy surgery (IES) and other surrogate marker of severe epilepsy on VNS effectiveness. The study included 376 patients (188 females; 265 adults; mean age of 29.4 years at implantation) with treatment resistant epilepsy (TRE) who underwent VNS implantation and had at least 1 year of follow-up. One hundred ten patients (29.3%) had failed one or more prior craniotomies for TRE and 266 (70.7%) had no history of IES. The mean duration of VNS therapy was 5.1 years. Patients with prior IES were more commonly male and adult, had a greater number of seizure types, and more commonly had focal or multifocal versus generalized seizures. There was no significant difference in the mean percentage seizure reduction between patients with and without a history of IES. There was no correlation between type of failed IES (callosotomy versus resection) and seizure reduction with VNS therapy. The authors concluded that failed IES did not affect the response to VNS therapy. Unlike prior reports, patients with callosotomy did not respond better than those who had resective surgery. Nearly 50% of patients experienced at least 50% reduction in seizure frequency. The authors stated that VNS should be considered a palliative treatment option for patients with TRE, including patients who failed cranial epilepsy surgeries.

There is evidence that the use of VNS provides significant health benefits for refractory seizures in pediatric patients. Elliott et al. (2011c) analyzed the efficacy of vagus nerve stimulation (VNS) in a large consecutive series of children 18 years of age and younger with treatment-resistant epilepsy and compared the safety and efficacy in children under 12 years of age with the outcomes in older children. The authors retrospectively reviewed 141 consecutive cases involving children (75 girls and 66 boys) with treatment-resistant epilepsy in whom primary VNS implantation was performed and who had at least 1 year of follow-up since implantation. The patients' mean age at vagus nerve stimulator insertion was 11.1 years (range 1-18 years). Eighty-six children (61.0%) were younger than 12 years at time of VNS insertion (which constitutes off-label usage of this device). 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. 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). The authors concluded that vagus nerve stimulation is a safe and effective treatment for treatment-resistant epilepsy in young adults and children. The authors state that given the efficacity 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.

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

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

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

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

- VNS may be considered as adjunctive treatment for children with partial or generalized epilepsy (level C). VNS was associated with a greater than 50% reduction in seizure frequency in 55% of 470 children with partial or generalized epilepsy (14 class III studies) but there was significant heterogeneity in the data.
- VNS may be considered in patients with Lennox-Gastaut syndrome (LGS) (level C). VNS was associated with a greater than 50% seizure reduction in 55% of 113 patients with LGS (4 class III studies).
- VNS may be considered progressively effective in patients over multiple years of exposure (level C).
- There should be extra vigilance in monitoring for occurrence of site infection in children. There is evidence of an increase in infection risk at the VNS implantation site in children relative to that in adults.

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

Depression

D01 – D06 Studies Reported to the FDA
Most of the available evidence regarding the safety and efficacy of VNS for depression comes from studies funded by or performed in collaboration with Cyberonics, Inc. Data from these studies were presented to the U.S. Food and Drug Administration (FDA) to support the Premarket Approval (PMA) application. Overall, six studies were performed, designated D01 to D06. Complete data sets have not been published for all of the studies. In these studies, VNS was performed using the NeuroCybernetic Prosthesis (NCP®) System, also referred to as the VNS Therapy™ System.

The D01 study was a prospective, open-label, nonrandomized, uncontrolled clinical study. The earliest D01 study initially enrolled 30 patients and was reported by Rush et al. (2000). Their results suggest that VNS provided symptom relief in 40% of the patients with major depression.
and bipolar disorders and that an additional 16% of the patients had remission of symptoms following VNS. The study limitations include lack of control group, small sample size, lack of power analysis and ten week follow-up. An additional 30 patients were enrolled and results were reported by Sackheim et al. (2001). They concluded that mean time from response to treatment was 48.1 days. Based on the HDRS and MADRS, the results were 30.5%-34% at the 10 week follow-up. Remission was reported in 15.3% of the patients. Lack of a control or comparator group, small sample size, and short follow-up compromised the quality of this study.

Marangell et al. (2002) (D01 trial) studied the effectiveness of twelve months of VNS therapy in the 30 patients that were enrolled in the Rush (2000) study. Twelve of the patients had greater than or equal to 50% improvement on the HDRS and 15 showed the same level of improvement on the MADRS. Approximately 29% of the patients achieved remission in this time frame. Limitations of this study included lack of control group, small sample size, and lack of statistical power analysis.

Nahas, et al. (2005) (D01 trial) completed a two year outcome study of 60 patients with VNS for the treatment of major depressive episodes. The results indicate that remissions rates were 15% at 3 months, 27% after 12 months and 22% after 2 years. Response rates were 31%, 44% and 42% at 3 month, 12 month and 24 month respectively. The authors concluded that the VNS treatment may show long term benefit. The lack of a control group, the concurrent medication therapy and financial relationship with the manufacturer limits the validity of the results.

In a randomized, sham-controlled clinical trial, Rush, et al. (2005a) (D02 trial) reported on vagus nerve stimulation that involved 235 patients with major depressive disorder or depressed phase bipolar disorder. All patients had a VNS implanted. After two weeks, the unit was activated in half of the patients. The patients were evaluated ten weeks later. After ten weeks, 15% of the active treatment and 10% of the sham treatment showed a response. It is noted that evaluation occurred in 222 patients without explanation of what happened to the balance of the participants. The authors concluded that VNS did not demonstrate short term efficacy in the treatment of depression. These same authors completed a twelve month follow up study of 205 of the same patients. (Rush, 2005b) The previously treated patients received another 9 months of VNS and the participants in the sham group received 12 months of VNS. The results showed a 27% response rate and a 15.8% remission rate. This study was flawed by the concomitant use of antidepressants and adjusted treatments of both the VNS and drugs during the study period and the lack of comparative group. Thirty of the participants required hospitalization for worsened depression. The authors concluded that VNS was well tolerated but that comparative long term data are needed to determine if the benefits are attributable to VNS.

Nierenberg et al. (2008) (D02 trial) described the outcome of VNS for bipolar treatment-resistant depression (TRD) patients participating in the acute and longitudinal pivotal trials and compared their outcome with unipolar TRD patients in the same trials. Of 235 participants enrolled in the acute study, 25 (11%) were diagnosed with DSM-IV bipolar I or II disorder. A sham-controlled 12-week trial of VNS preceded 2 years of open treatment. Bipolar and unipolar subjects were compared on baseline characteristics as well as acute and long-term outcomes. At baseline, bipolar TRD was as severe as unipolar TRD but with depressive episodes of shorter duration and more failed antidepressant trials/year. Acute, 1-year, and 2-year outcomes were similar for both groups, even when the definition of response for bipolar TRD was expanded to include lack of manic symptoms. The study reported that 33% of patients with unipolar depressive symptoms and 38% of patients with depressive bipolar disease demonstrated a response at 24 months compared with baseline. According to the investigators, in this hypothesis-generating analysis, VNS short- and long-term effects on bipolar and unipolar TRD were similar. Because these analyses were post hoc, these findings should not be interpreted as warranting clinical inference regarding effectiveness of VNS in patients with bipolar depression.

A case series that included 74 patients with treatment resistant depression found a 34% response rate to VNS at 3 months (end of active treatment period), which increased to 47% at the 12 month follow-up (Schlaepfer, 2008) (D03 trial). There was no comparison group in this study, so response with a different treatment or no treatment is not known. Also, patients were not blinded,
Clinical studies included reported no

Vagus Nerve Stimulation

Generally, VNS is reported to be a safe and feasible procedure, de

short and long term. Unfortunately, the only double

of the depressive symptoms (primary outcome: Hamilton Depression Rating Scale, HDRS) in the

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September 2007. Ninety

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explained by baseline severity of depression. The authors stated that insufficient data are

determination was 0.84, which implies that an 84% var

the cause of this heterogeneity, a meta

response and remission rates in

depressed patients with chronic treatment-resistant depression (TRD) treated with vagus nerve stimulation (VNS) plus treatment as usual (VNS + TAU) or TAU. The six clinical studies included in the meta-analysis were two single-arm studies of VNS + TAU, a randomized trial of VNS + TAU versus TAU, a single arm study of patients who received TAU, a randomized trial of VNS + TAU comparing different VNS stimulation intensities, and a nonrandomized registry of patients who received either VNS + TAU or TAU. Response was based on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions scale's Improvement subscale (CGI-I), as these were the two clinician-rated measures common across all or most studies. Outcomes were compared from baseline up to 96 weeks of treatment with VNS + TAU (n = 1035) versus TAU (n = 425). MADRS response rate for VNS + TAU at 12, 24, 48, and 96 weeks were 12%, 18%, 28%, and 32% versus 4%, 7%, 12%, and 14% for TAU. The MADRS remission rate for VNS + TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14% versus 1%, 1%, 2%, and 4%, for TAU. Adjunctive VNS Therapy was associated with a greater likelihood of response and remission compared with TAU. For patients who had responded to VNS + TAU at 24 weeks, sustained response was more likely at 48 weeks and at 96 weeks. Similar results were observed for CGI-I response. The authors concluded that for patients with chronic TRD, VNS + TAU has greater response and remission rates that are more likely to persist than TAU. According to the authors, the primary limitation of the meta-analysis involved the individual study designs; namely, that the TAU group data is limited to two trials for the CGI-I scale and one trial for the MADRS scale; in addition, the nonrandomized study and the randomized, sham-controlled study represent the only concurrent head-to-head comparisons of VNS + TAU and TAU.

Martin and Martin-Sanchez (2012) conducted a systematic review and meta-analysis of analytical studies to determine the efficacy of vagus nerve stimulation (VNS) for treatment of depression. Fourteen studies met the selection criteria and were included in the review. 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%. 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. To study the cause of this heterogeneity, a meta-regression was performed. The adjusted coefficient of determination was 0.84, which implies that an 84% variation in effect size across the studies was explained by baseline severity of depression. The authors stated that insufficient data are available to conclude whether or not VNS is 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.

Daban et al. (2008) evaluated the safety and efficacy of vagus nerve stimulation (VNS) in treatment-resistant depression (TRD) by means of systematic review using the major databases (Medline, Psychological Abstracts, Current Contents), beginning in January 2000 and ending in September 2007. Ninety-eight references were found, but only 18 add-on studies (n=1251) met the required quality criteria and were included in the review. Only one double-blind, randomized study was available and therefore a meta-analysis was not feasible. In a majority of the preliminary open studies selected for the review, VNS was associated with a significant reduction of the depressive symptoms (primary outcome: Hamilton Depression Rating Scale, HDRS) in the short and long term. Unfortunately, the only double-blind study gave rather inconclusive results. Generally, VNS is reported to be a safe and feasible procedure, despite its invasive nature. The
authors 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 needed to confirm its efficacy in major depression.

In a multicenter, double blind study, Aaronson et al. (2013) compared the safety and effectiveness of different stimulation levels of adjunctive vagus nerve stimulation (VNS) therapy for the treatment of treatment-resistant depression (TRD). A total of 331 patients with TRD were randomized to one of three dose groups: Low (0.25 mA current, 130 μs pulse width), Medium (0.5-1.0 mA, 250 μs), or High (1.25-1.5 mA, 250 μs). A highly treatment-resistant population (>97% had failed to respond to ≥6 previous treatments) was enrolled. Response and adverse effects were assessed for 22 weeks (end of acute phase), after which output current could be increased, if clinically warranted. Assessments then continued until week 50 (end of long-term phase). During the acute phase, all groups showed statistically significant improvement on the primary efficacy endpoint (change in Inventory of Depressive Symptomatology-Clinician Administered Version [IDS-C]), but not for any between-treatment group comparisons. In the long-term phase, mean change in IDS-C scores showed continued improvement. Post-hoc analyses demonstrated a statistically significant correlation between total charge delivered per day and decreasing depressive symptoms; and analysis of acute phase responders demonstrated significantly greater durability of response at Medium and High doses than at the Low dose. The authors concluded that TRD patients who received adjunctive VNS showed significant improvement at study endpoint compared with baseline, and the effect was durable over 1 year. The lack of a controlled standard treatment comparator group limits the conclusions that can be reached from this study.

In a small, prospective, nonrandomized, controlled study, Sperling et al. (2009) measured improvement in depression (HDRS28) for 12 months. Changes in the duration of depression-related hospitalization and the number of psychiatric treatments per year were also evaluated. The study enrolled 9 patients receiving VNS as an adjunct to pharmacotherapy and psychotherapy and 9 patients, sex-matched and age-matched to the VNS group, who continued pharmacotherapy and psychotherapy but did not undergo device implantation. VNS significantly improved HDRS28 scores from 23.7 to 10.2 points at 12 months. There was no significant change in the control group. VNS also significantly decreased the yearly number of days hospitalized from 65 to 44, while the hospitalization rate in the control group did not change. VNS also reduced the number of psychiatric treatments from 33 to 24 per year. There was no statistically significant change in this parameter for the control group. The respective values for the control group were 24.9 and 25.3 treatments per year. While the study results suggest that VNS may improve depression, the study used only one instrument to assess this outcome and did not include a sham control; therefore, the result must be interpreted with caution since a placebo effect may have confounded the results. However, the additional outcomes, duration of hospitalization, and number of psychiatric treatments are indirect measures, suggesting that VNS may improve depression severity. Nevertheless, the small sample size and lack of blinded assessment are additional factors compromising the quality of the evidence.

Bajbouj et al. (2010) assessed the efficacy and the safety of VNS in 74 patients with therapy-resistant major depressive disorder. Psychometric measures were obtained after 3, 12, and 24 months of VNS. Mixed-model repeated-measures analysis of variance revealed a significant reduction at all the 3 time points in the 28-item Hamilton Rating Scale for Depression (HRSD28) score, the primary outcome measure. 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 2-year open-label trial suggest a clinical response and a comparatively benign adverse effect profile among patients with treatment-resistant depression. The lack of a control group limits the validity of the results of this study.

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

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

The clinical evidence was reviewed in August 2015 with no additional information identified that would change the conclusion for depression.

Professional Societies

American Psychiatric Association (APA): In a clinical practice guideline for the treatment of patients with major depressive disorder, the APA states that electroconvulsive therapy remains the treatment of best established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared. The APA states that vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of 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)

Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT): In 2008-2009, the Canadian Psychiatric Association and the CANMAT partnered to produce evidence-based clinical guidelines for the treatment of depressive disorders. Among the four forms of neurostimulation for depression 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 much smaller 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 investigators 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. Evidence to support VNS is less robust and deep brain stimulation remains an investigational treatment (Kennedy, 2009).

Other Conditions

The use of vagus nerve stimulation has been investigated for other conditions including Alzheimer’s disease (Merrill et al. 2006), anxiety (George, 2008), autism spectrum disorder (Levy, 2010), obsessive-compulsive disorder (George et al. 2008), pain (Napadow et al. 2012; Ness et al. 2000), headaches (Straube et al. 2015; Cecchini et al. 2009; Mauskop, 2005; Hord et al. 2003), obesity (Ikramuddin et al. 2014; Sarr et al. 2012; Pardo et al. 2007), sleep disorders (Marlow, 2001), heart disease/congestive heart failure (Zannard et al. 2015; Premchand et al. 2002).
2014; Deferrari et al. 2011), asthma (Steyn et al. 2013; Miner et al. 2012), and fibromyalgia (Lange et al. 2011). However, because of limited studies, small sample sizes and weak study designs, there is insufficient data to conclude that vagus nerve stimulation is safe and/or effective for treating these indications. Further clinical trials demonstrating the clinical usefulness of vagus nerve stimulation are necessary before it can be considered proven for these conditions.

Additional Search Terms
Lennox-Gastaut syndrome, neuromodulation, pneumogastric nerve, vagal stimulation.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

The FDA approved the NeuroCybernetic Prosthesis (NCP)® System (Cyberonics, Inc.) in July 1997 (P970003) for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with medically refractory, partial-onset seizures. Since the original approval, there have been a number of modifications to the device, the instruments used to implant the electrodes and the stimulator, and the software used to control and program the stimulator. The NCP System cannot be used in patients after a left or bilateral cervical vagotomy. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/p970003.pdf Accessed August 2015.

In August 2001, manufacturers of neurostimulation devices advised against the use of shortwave, microwave or therapeutic ultrasound diathermy for persons implanted with the devices. Diathermy may potentially cause the generator or leads to heat up and damage tissue, causing pain and discomfort.


In July 2005, the VNS Therapy™ System (Cyberonics, Inc.) was approved for marketing by the FDA for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. (PMA Supplement 50) Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/Device%20ApprovalsandClearances/Recently-ApprovedDevices/ucm078532.htm.

On January 14, 2015, the FDA approved the Maestro® VNB system for use in patients 18 years or older who have been unable to lose weight with a weight-loss program and who have a BMI of at least 40 kg/m² or greater than 35 kg/m² with at least 1 other obesity-related condition. As part of the Maestro system approval, the manufacturer must conduct a five-year postapproval study that will follow at least 100 patients and collect additional safety and effectiveness data, including weight loss, adverse events, surgical revisions and explants, and changes in obesity-related conditions.


To locate marketing clearance information for a specific device or manufacturer, search the Center for Devices and Radiological Health (CDRH) 510(k) database or the Premarket Approval (PMA) database by product and/or manufacturer name. Use product code LYJ (stimulator, autonomic nerve, implanted for epilepsy).
REFERENCES

The foregoing Oxford policy has been adapted from an existing United-Healthcare national policy that was researched, developed and approved by United-Healthcare Medical Technology Assessment Committee [2015T0101T].


**POLICY HISTORY/REVISION INFORMATION**

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<th>Date</th>
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| 12/01/2015 | • Updated coverage rationale; reformatted list of proven/medically necessary indications  
|            | • Updated list of applicable HCPCS codes; removed L8681                                   
|            | • Updated supporting information to reflect the most current clinical evidence, FDA information, and references   |
|            | • Archived previous policy version SURGERY 073.11                                        |