Vagus Nerve Stimulation for Treatment of Epilepsy

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EPILEPSY BOARD REVIEW MANUAL

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Statement of Editorial Purpose

The Epilepsy Board Review Manual is a study guide for trainees and practicing physicians preparing for board examinations in epilepsy. Each manual reviews a topic essential to the current management of patients with epilepsy.

Note from the Publisher

This publication has been developed without involvement of or review by the American Board of Psychiatry and Neurology.

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Drug-resistant epilepsy is not a benign disease. Patients often develop depression and anxiety and have immense morbidity associated with their disease.\(^1\) Mortality rates in persons with drug-resistant epilepsy are higher than in the general population.\(^2\) When medications alone are not effective and resective brain surgery is not a good option, alternative therapies for epilepsy such as vagus nerve stimulation (VNS) should be considered. Since 1988, more than 80,000 patients worldwide have been implanted with a VNS device.

VNS is part of the growing field of neuromodulation. This class of therapy is usually delivered through an implanted device. The main goal is to target a specific area within the nervous system to modulate or balance the neural circuitry and manage clinical symptoms. The pivotal trials of VNS therapy used it to deliver, in an open-loop fashion, continuous but intermittent (“on” and “off” cycles) stimulation of the left vagus nerve. This type of stimulation has resulted in significant seizure reduction in the majority of patients. Furthermore, a device recently approved in Europe and the United States adds automatic stimulation based on a pre-programmed level of ictal tachycardia (sensing algorithm) to help control seizure frequency and duration. This article discusses the indications, surgical technique, and clinical data to support VNS use in medically resistant epilepsy.

### TECHNICAL ASPECTS

The VNS Therapy System (Cyberonics, Webster, TX) is composed of a generator attached to a bipolar helical lead (Figure). Interrogation and programming is carried out via an external programming wand connected to a handheld computer.

Insertion of the device requires a minimally invasive procedure that is done under general anaesthesia and usually involves 1 or 2 incisions (depending on surgeon’s preference).\(^3,4\) The cervical incision is carried out in a natural crease for cosmetic purposes, if possible. The platysma muscle is divided and, using blunt and sharp dissection, the carotid sheath is exposed. The vagus nerve is usually deep to the vascular structures within the sheath, and at least 2.5 cm of the nerve is exposed. The lead (stimulating electrode) is then attached to the left vagus nerve under loop magnification. The cable leading to the generator is tunnelled in the subcutaneous fat layer. A subcutaneous pocket in the anterior chest wall is made for the generator. Typically, the generator has to be replaced every 5 to 7 years, depending on activation parameters, but newer models are expected to last longer (up to 10 years). This procedure requires outpatient surgery.

Stimulation can be commenced postoperatively, but a waiting period of 10 to 14 days is usually allowed for wound healing. The generator delivers a biphasic current that continuously cycles between on and off periods. Typically, the current output is adjusted to tolerance, using a 30-Hz signal fre-
quency with a 500-μs pulse width for 30 seconds of on and 5 minutes of off time. These default settings were used in the initial double-blind studies involving patients who were assigned randomly to receive high levels of stimulation. In clinical practice, the stimulation parameters are started low (0.25 mA) and gradually increased every few weeks based on clinical response and tolerability.

Patients may initially feel the stimulation (mild throat discomfort, cough, voice change), and if they find this uncomfortable the device parameters can be altered. The threshold for adverse effects is highly variable, but typically patients will adjust over time. A multicenter, randomized trial of VNS was performed to try to identify the optimal stimulation parameters. However, these results showed no major outcome difference in the different groups and the data supports the use of standard duty-cycles as initial therapy. A recent review suggests that the data remains limited to support any other parameter settings and proposes that rapid cycling may increase the need for battery replacement, providing another reason to utilize standard duty-cycles. Although some studies have shown a tendency for better seizure control with higher settings, these settings are associated with an increased rate of adverse effects. In summary, there is no clear evidence that higher stimulation intensity or rapid cycling is more effective.

A handheld magnet is given to the patient or the patient’s caregiver following placement of the VNS device. For those patients who can sense the beginning of a seizure, the magnet can be used for “on-demand” stimulation. If stimulation is performed at seizure onset, then the episode can be modulated (intensity) or even terminated (seizure duration) via this process. This mode of on-demand stimulation offers more control to patients and families and improves post-ictal recovery.

Intraoperative complications for VNS surgery are low. Unique to this device is the potential for transient and permanent vocal cord paralysis secondary to recurrent laryngeal nerve stimulation or damage. The incidences of bleeding, infection, and permanent vocal cord paralysis are less than 3%. The risk for infection seems to be slightly higher in children as compared with adults. The main adverse effects secondary to the stimulation are very mild, transient, and usually do not interfere with quality of life. In the initial studies of VNS therapy (Vagus Nerve Stimulation Study Group E03 and E05), patients who received higher levels of stimulation were more predisposed to suffer from these adverse effects. Voice alteration (13%–37%) and throat pain (10%–29%) are the most frequent complaints. Less commonly, cough, paresthesias, dyspnea, nausea, and chest pain have been described. However, the hand-held magnet can be used to minimize adverse effects.
If the magnet is held (or taped) over the generator, the stimulation will stop temporarily, which may be beneficial in certain situations or activities such as public speaking or singing.

A very small number of patients describing transient rhythmic irregularities have been reported. However, none of these demonstrated major permanent cardiac dysfunction. It is believed that the left vagus nerve has fewer cardiac and autonomic connections than the right vagus nerve. The fact that impulses to the sinoatrial node travel principally through the right vagus nerve provides justification for left-sided placement of these implants.

Electrical stimulation of no more than 3.5 mAmp is delivered to the vagus nerve. The stimulation frequency recommended and generally used has not produced any documented tissue damage. In addition, safety measures have been adapted to the device. The VNS Therapy System is not affected by microwaves, cellular phones, or airport security systems. Some restrictions do apply to the use of magnetic resonance imaging (MRI). Because of the potential for tissue damage with a body MRI, MRI should be used only for head imaging and a transmit and receive head coil should be used; also, the device should be turned off during imaging. The VNS Therapy System (generator and lead) must not be exposed to a radiofrequency field.

MECHANISM OF ACTION

The cervical portion of the vagus nerve is mainly composed of afferent connections (80% of fibers) and contains a mix of A-, B-, and C-fibers (histopathologically defined by diameter and degree of myelination). The lowest-amplitude stimulation occurs with the A-fibers (heavily myelinated), and this represents the most likely pathway for action potential activation with the stimulation. This is reinforced by the fact that chronic stimulation does not typically cause bradycardia, since the C-fibers (carrying parasympathetics) are unaffected. The nucleus solitarius (NTS) receives the majority of vagal afferent synapses. The NTS has direct or indirect projections to the locus coeruleus, raphe nuclei, reticular formation, and other brainstem nuclei and thus modulates norepinephrine and serotonin release. These neurotransmitters ultimately have effects on the limbic, reticular, and autonomic centers of both cerebral hemispheres.

The pivotal studies by Bailey and Bremore in 1938, and subsequently by Dell and Olson in 1951, demonstrated that VNS influences cerebral activity. Stimulation of the cut end of the vagus nerve evoked response in the ventroposterior and intralaminar regions of the thalamus. Through a thalamic pathway this afferent connection modified neuronal activity at the level of the cerebral cortex. Those findings were documented in the electroencephalogram (EEG). In 1952, Zanchetti and colleagues demonstrated the ability of VNS to eliminate interictal epileptic events in a chemically induced seizure model in cats. In the following decades, many experiments were conducted, mostly using cat models, that further confirmed the potential of VNS to decrease epileptic activity. Zabara in 1985 reported the effects of stimulation of the vagus nerve on seizure control in animal studies. It was proposed...
that cervical region stimulation of the nerve might attenuate seizures by desynchronizing the cerebral cortical activity. Therefore, it was postulated that afferent vagal synapses attenuate seizure activity through neurotransmitter modulation.\textsuperscript{22,24} In addition, Naritoku and colleagues studied the molecular biological effects of VNS on multiregional neuronal activities in the brainstem and cerebral cortex.\textsuperscript{25} This group demonstrated that intermittent VNS increases expression of neuronal fos (a marker for increased metabolic activity) in the medullary vagal complex, locus coeruleus, and several diencephalic nuclei. Other described effects of stimulation include overexpression of brain-derived neurotrophic factor and fibroblast growth factor (especially in the hippocampus and cerebral cortex), decreases in the quantity of nerve growth factor mRNA in the hippocampus, and surges in the norepinephrine concentration in the prefrontal cortex.\textsuperscript{26} It has been suggested that VNS works by increasing cerebral blood flow and activating neuronal networks in the thalamus and other deep brain structures. This activity affects neurotransmitters, including serotonin and norepinephrine, which are implicated in depression.

Three temporal patterns of seizure control have been detected in animal studies (Table). These mechanisms include the acute abortive effect, the acute prophylactic effect, and the chronic progressive prophylactic effect. Acute abortive effect describes a situation in which the acute insult was applied to the cerebral cortex with subsequent cessation of cortical excitability.\textsuperscript{22,23,27} In addition, Lockard and colleagues\textsuperscript{28} and Woodbury and Woodbury\textsuperscript{29} have shown that VNS can decrease seizure frequency and severity. Chronic prophylactic antiseizure effect was confirmed in the primate model, where the antiseizure effects of VNS continued to increase after days and weeks of stimulation.\textsuperscript{28,30} Likewise, stimulation of the vagus nerve was found to interfere with epileptogenesis in the cat (amygdala kindling model).\textsuperscript{31}

Despite extensive experimental work, the precise mechanism by which VNS therapy confers antiseizure effects remains poorly understood. Though some studies have demonstrated spike reductions using VNS,\textsuperscript{28} this decline did not correlate with seizure reduction, and a clear EEG pattern has not been demonstrated during VNS therapy.\textsuperscript{32} In summary, VNS therapy alters cerebral electric-
cal activity and cerebral blood flow causing an activation of neuronal networks via thalamocortical pathways (it can be reasonably assumed to involve brainstem nuclei), but the detailed mechanism of action has yet to be elucidated.

**CLINICAL DATA**

The first VNS implants were performed in 1988. This event was followed by 2 pilot studies (E01, E02) in 15 patients. A programmable stimulating device initially called the NeuroCybernetic Prosthesis (NCP) was implanted to stimulate the cervical vagus nerve. Patients were followed for at least 35 months and the results demonstrated a seizure reduction of 46.6%. Minimal adverse effects were encountered.

Due to the success and safety profile documented in the early studies, a randomized active control study (E03) was performed in 1992, which demonstrated a 24.5% mean reduction in seizure frequency in patients who received high-level stimulation (presumed therapeutic dose). The European Community approved the use of the NCP for VNS in the treatment of medically resistant epilepsy in 1994. The results of another pivotal study (E05) involving 198 patients were published in 1998. These patients were randomized to either a high stimulation group (HSG) (n = 95) or a low stimulation group (LSG) (n = 103). The mean decrease in seizure frequency was 28% in the HSG group versus 15% in the LSG group (P = 0.039) at 3 months. More important, a reduction in seizure frequency greater than 75% was noted in 11% of the HSG group. A follow-up study was completed after the initial phase of the E05 trial. Because the preliminary findings demonstrated a better clinical response in the HSG group, all 195 patients in the long-term follow-up study received VNS using the high-stimulation parameters. At 12 months follow-up after completion of the acute phase of the E05 trial, the mean reduction of seizure frequency was 45%. More significant, 35% had a reduction of at least 50%, and 20% had a reduction of at least 75%. More clinically important was the finding that device parameter changes were not a predominant predictor of increased efficacy. These studies attested to the safety, efficacy, and tolerability of VNS in the management of medically refractory epilepsy. In 1997, the US Food and Drug Administration (FDA) approved the use of this device as an adjunct to medical therapy for refractory epilepsy in adults and adolescents older than 12 years.

Long-term outcome studies have found a greater than 50% reduction in seizures in at least 40% of patients with a 3-year follow-up. Another retrospective study, with a 12-year follow-up, found a mean seizure reduction of 26% after 1 year, 30% after 5 years, and 52% after 12 years. Additionally, Elliott et al found that seizure reduction improves over time and is sustained for at least 10 years post-VNS therapy. These studies and another series demonstrated that neuromodulation with VNS has a prolonged and persistent benefit for refractory epilepsy, with long-term seizure reduction of 50% or more in approximately 50% of patients. It may take anywhere from several months to several years for patients to obtain the full extent of seizure reduction from VNS therapy.

In addition to the prolonged benefit of stimulation, there is the potential for drug reduction in this population, which has the added gain of decreased polypharmacy and its adverse effects. Likewise, Amar and colleagues found that in a group of 3822 patients the median reduction in seizure frequency was 66.7% at 24 months for those patients who had not undergone previous cranial surgery. However,
in patients with previous surgical therapy (n = 921) there was a significant but not as dramatic improvement (50.5% median seizure reduction). These data demonstrated that patients in whom prior cranial surgery had failed did not respond as favorably as all other patients receiving VNS therapy but that VNS still represents a potentially palliative treatment option for patients with refractory seizures after failed resective brain surgery.

Improvements in quality of life measures have been demonstrated in 30% to 60% of patients with epilepsy treated with VNS therapy. In a long-term, open-label, randomized, parallel-group study of VNS therapy versus AEDs alone in 112 patients with medically resistant epilepsy, there was a statistically significant difference in quality of life (Quality of Life in Epilepsy Inventory [QOLIE]-89 total score) in patients receiving VNS therapy.43 Considerable interest has focused on improvements in mood in patients with epilepsy treated with VNS. Multiple studies, including the international multisite randomized double-blind trial on seizure control by VNS (E03), have demonstrated significant positive mood effects, which were independent of effects on seizure activity.44,45 VNS therapy is associated with improvements in both mood and quality of life in patients with refractory epilepsy. Since these improvements appeared to be independent of seizure control, they indicate an additional antidepressant effect of VNS, which can be of value in the management of mood disturbances in patients with epilepsy. More important, another study found that the rates of sudden unexpected death in epilepsy (SUDEP) in patients treated with VNS therapy dropped from 5.5 per 1000 person-years in the first 2 years of VNS therapy to 1.7 per 1000 person-years after that (n = 1819 followed for 3176.3 person-years from date of implantation).6

More recent data examining the long-term outcome of VNS for patients in whom epilepsy surgery failed have shown modest but persistent results. A group of 37 patients in whom initial surgical management failed underwent VNS placement and were followed for at least 18 months with attention focused on seizure burden, AED burden, and quality of life measures. Results demonstrated that 64.9%, 24.3%, and 10.8% of patients achieved a subjective reduction in seizure frequency of less than 30%, 30% to 60%, or greater than 60%, respectively, after VNS placement. In addition, there was a modest decrease in AED requirements. More clinically significant, 45.9% of patients subjectively reported quality of life as being “better” or “much better.”46 Other studies have demonstrated median seizure reduction as high as 50% after 24 months.42

Even in those patients who required revision surgery for lead break or damage, there is enough clinical evidence to suggest persistent benefits from VNS therapy.47 A recent retrospective study to assess seizure and psychological outcomes found that a large majority of patients (80%) considered VNS therapy worthwhile even in those cases with modest seizure reduction.48 In a retrospective study, pre- (6 months) and post- (up to 3 years) analysis of VNS implantation using multistate Medicaid data from January 1997 to June 2009 (n = 1655) found that resource utilization and epilepsy-related clinical events were significantly reduced in this population.49 More significant is the finding that hospitalizations, especially seizure-related hospitalizations, and emergency department visits dropped by more than 40%, with a smaller reduction in outpatient visits.

The use of VNS in children younger than the FDA-approved 12 years or older criterion is more limited, but reports of VNS efficacy in this group
are encouraging. Saneto et al studied 43 children with medically resistant epilepsy, finding a median 55% reduction rate in seizures after 12 months. Healy and colleagues found VNS therapy to be safe and effective for children under 12 years old, with greater than half (56%) having a seizure reduction of greater than 50%. In a 2-year follow-up study, 347 children were enrolled to assess seizure outcome after VNS. The authors followed these patients at 6, 12, and 24 months after implantation and found a seizure reduction rate of greater than 50% in 32.5%, 37.6%, and 43.8%, respectively, without any major significant adverse effects. Elliott et al followed 141 cases of children, 61% of whom were younger than 12 years old at the time of insertion, and found no difference in efficacy or complications as compared to the group comprising children aged 12 years and older.

VNS therapy has additional beneficial effects in children with intractable epilepsy. In contrast to AEDs, there are no documented negative side-effects on cognition. Furthermore, improvement of mood in general and depressed feelings in particular have been demonstrated, irrespective of a reduction in seizure frequency.

**INDICATIONS**

When VNS was approved in the United States by the FDA in 1997, as noted, the initial indication was labelled as an “adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications.” However, there is increasing evidence that VNS is effective in the symptomatic generalized epilepsies, refractory idiopathic (primary) generalized epilepsies, Lennox–Gastaut epilepsy, absence epilepsy, in the pediatric population, and in other seizure disorders for which there are limited therapeutic alternatives. In addition, VNS therapy is indicated as an adjunctive long-term therapy of chronic or recurrent depression for patients 18 years or older who have not had an adequate response to multiple antidepressants.

It is generally accepted that prolonged EEG-video monitoring should be performed before implantation of the VNS device. Clinical evidence suggests that approximately 30% of patients with suspected intractable seizures may have psychogenic nonepileptic seizures. In addition, another 30% of patients could be candidates for resective brain surgery, which is generally considered to be more effective than VNS therapy. As an example, in cases of lesional epilepsy or medically resistant mesial temporal lobe epilepsy, surgery should be considered the therapy of choice. By contrast, in non-lesional extratemporal epilepsy or failed epilepsy surgery, VNS is an acceptable treatment option. In the end, these options are a matter of risk-benefit ratio and need to be discussed with the patient and family. The decision to proceed with VNS therapy should be made only after prolonged video-EEG recording.

**NEW APPLICATIONS**

VNS therapy is usually delivered in an “open-loop” fashion. It is continuous but intermittent (“on” and “off” cycles) without any feedback. This type of stimulation is blind and may be of limited benefit for those patients unable to use the hand-held magnet due to the clinical semiology (unaware of seizures), nocturnal seizures, immobilization due to physical conditions, or cognitive impairment. Another class of neuromodulation uses a closed-loop system. This type of stimulation reacts to...
bursts of stimulus (detection), and may be better tolerated due to lower current thresholds. In theory, this device could be a more efficient delivery system for stimulation. With this scientific principle in mind, an automated seizure detection device (AspireSR, Cyberonics, Houston, TX) has been designed and recently tested. Algorithms based on changes in heart rate at or near the onset of the seizure may provide a methodology for automated responsive stimulation.

Eggleston and colleagues performed a scientific data review and found that the current literature supports the occurrence of significant tachycardia associated with ictal events in those patients (82%) with documented EEG and electrocardiogram (ECG). Despite the intra-individual variability, no clinically significant differences were demonstrated in generalized or partial onset seizures. In a single-case publication, Hampel et al found that heart rate–triggered VNS therapy significantly reduced seizure duration. However, despite good sensitivity (92%) in recognizing the epileptic events, there was low specificity (13.5%). Another pilot study found the intraoperative handling and technique are equivalent to former models. However, the placement of the generator is generally more medial in the chest wall area (for better cardiac detection), which might cause cosmetic issues and requires discussion with the patient. A prospective, multicenter study was performed in Europe using cardiac-based seizure detection to activate the VNS device. Thirty-one patients were enrolled and followed for 12 months. Patient-scored seizure severity (total SSQ score) showed significant improvement at 6 months. In addition, quality of life (total QOLIE-31-P score) was also significantly improved at 12 months. More significant, in 10 of 17 epileptic events where triggered VNS overlapped with ongoing seizure activity, the seizure aborted during stimulation. Good outcomes (greater than 50% seizure reduction) were documented in 29.6% of the patients at 12 months. Again, sensitivity was high, but the specificity was low for this patient population. They concluded that this mode of therapy is safe and a combination of open- and closed-loop stimulation may be beneficial for medically resistant epilepsy.

**CASE PRESENTATION**

A 16-year-old girl with a history of congenital rubella and associated cognitive impairment is referred for evaluation of medically refractory seizures. Her family has recently moved to a new location and is looking for a neurologist to treat her seizures. She has frequent brief spells (approximately 5–8/week) and occasionally tonic-clonic activity that may last up to 30 seconds. The patient is wheelchair bound due to the severity of her clinical condition. She is also congenitally blind. She has minimal interaction with the surroundings but responds to verbal stimuli from the caregiver. She is currently on 4 AEDs (Trileptal/Lamictal/Keppra/Valium). Head CT scan demonstrates peri-ventricular calcifications with stable but mild ventriculomegaly. The patient undergoes 1 day of continuous video-EEG recording without activation that demonstrates generalized bursts of high-amplitude spike/wave discharges lasting less than 3 seconds, rhythmic delta activity in the middle central regions, episodes of generalized paroxysmal fast activity during sleep, and rare multifocal spike/wave discharges. During the 24-hours of recording, no electrographic seizures are recorded.

Based on her current evaluation, she is not a good candidate for resective brain surgery. The best options include: maintaining or adding AEDs, ketogenic diet, or neuromodulation. Adding an-
other AED may not be beneficial for her condition due to the potentiation of adverse effects from polypharmacy (e.g., drowsiness). Her caregiver already complains of her limited interaction with family. Ketogenic diet is an option, but it requires family training and compliance with treatment (a frequent problem with teenagers, but she has limited cognitive capacity). The last option is neuromodulation. VNS therapy is a good treatment alternative (multiple focal spikes/generalized bursts of activity). Adverse effects in her situation are probably going to be minimal. VNS may result in decreased seizure frequency and improvement in quality of life. Responsive Neurostimulator (RNS) (Neuropace, Mountain View, CA) is another mode of neuromodulation (closed-loop system) that requires recording and stimulating intracranial electrodes. This therapy requires the identification of a seizure focus (or foci) by EEG monitoring. Based on this patient's electrophysiology, RNS is not a good alternative for her condition.

The patient undergoes placement of a VNS device. Six months after surgery, seizure frequency has decreased approximately 40% to 50%. More clinically significant is the fact that she is more active and alert. The caregiver feels that the patient’s and family’s quality of life is “much better” since device activation. If clinical improvement continues, then consideration can be given for drug reduction.

CONCLUSION

VNS therapy is a safe and effective treatment for patients with drug-resistant epilepsy who are not good surgical candidates. Although the mechanism is still poorly understood, several clinical trials have demonstrated its efficacy and safety. The main benefits from stimulation include better long-term seizure control and improved quality of life with the potential for decreased health care costs and utilization.

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