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VAGUS NERVE STIMULATION THERAPY 5 YEARS AFTER APPROVAL: A COMPREHENSIVE UPDATE

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Introduction

Articles

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The evolving place of vagus nerve stimulation therapy

Steven C. Schachter, MD; and James W. Wheless, MD

Article abstract—Approximately 40% of patients with epilepsy have seizures that do not adequately respond to medical therapy. Vagus nerve stimulation (VNS) therapy, approved 5 years ago by the Food and Drug Administration, offers a therapeutic option for patients with pharmacoresistant seizures. This supplement updates developments with VNS therapy since its approval and suggests future directions for this still-evolving treatment.

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In July of 1997, the United States Food and Drug Administration (FDA) approved the NeuroCybernetic Prosthesis, now known as the Vagus nerve stimulation (VNS) Therapy System (Cyberonics, Inc.; Houston, TX), "for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial seizures which are refractory to antiepileptic medications."[1] The VNS Therapy System thereby became the first device approved to treat epilepsy and is now implanted in approximately 16,000 patients.

Pharmacoresistant epilepsy can be characterized by an inadequate response to antiepileptic drug (AED) therapy.[2] In their recently published study, Kwan and Brodie[3] showed that 222 of 470 (47%) newly diagnosed epilepsy patients (median age 29; range 9 to 93) became seizure-free for at least 1 year with the first AED prescribed. Eventually, an additional 79 (17%) patients became seizure-free. The success of additional therapy (either substitution or addition of another AED) was related to the reason for failure of the initial treatment. Of the 113 patients whose seizures failed to improve with the first AED, only 12 (11%) achieved seizure freedom with the second drug. In contrast, of the 69 patients who tried a second AED because of intolerable side effects from the first AED, 28 (41%) became seizure-free, as did 16 (55%) of the 29 patients who had idiosyncratic reactions to the first AED. Furthermore, of the 470 patients in the study, only 18 (4%) patients became seizure-free with the third or multiple AEDs.

Kwan and Brodie's study suggests that adult patients with medically refractory seizures might be identifiable early in their course if several courses of appropriate AED treatment are unsuccessful.[3] Assuming that their study group is representative, our challenge lies in selecting other available therapies for the approximately 40% of patients with epilepsy with pharmacoresistant seizures.

The consensus of epilepsy experts for the treatment of three epilepsy syndromes—idiopathic generalized epilepsy, symptomatic localization-related epilepsy, and symptomatic generalized epilepsy—was recently published.[4] The experts agreed that a trial of AED monotherapy was appropriate as the first line of treatment for all three syndromes and that, if the first AED fails, monotherapy with another AED should be prescribed. Opinions differed regarding treatment after failure of the second AED. Some experts recommended additional trials of monotherapy, and others suggested trying a combination of two AEDs. Most experts agreed that additional combinations of two AEDs should be tried if the first combination failed, but they differed regarding subsequent actions. However, the experts did recommend evaluation for epilepsy surgery for patients with symptomatic localization-related epilepsy who had failed third-step therapy. The efficacy of epilepsy surgery in curtailing or reducing the frequency of seizures has recently received considerable attention.[5] Although seizure-free rates up to 85%[6] have been reported after surgery for localization-related epilepsy, the surgery entails some risk and many patients are not suitable candidates.

What impact will the new AEDs have? Lhatoo et al.[7] studied the effectiveness of lamotrigine, topiramate, and gabapentin as add-on therapy among patients with chronic refractory epilepsy. Less than one-third of the patients remained on one of these AEDs at a 3-year follow-up. Given this marked dis-

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continuation rate, the authors predicted that these three new AEDs will probably have limited long-term impact on the course of patients with chronic refractory partial epilepsy.

Clearly, the low likelihood of achieving seizure freedom after failure of the first two AEDs,[3] the low long-term continuation rate with newer AEDs,[7] the success of epilepsy surgery in selected cases,[6] and current expert opinion[4] suggest that nonpharmacologic therapies should be considered for patients whose seizures continue despite several courses of AEDs. Fortunately for these patients, recent advances in non-AED therapies such as vagus nerve stimulation (VNS), the ketogenic diet,[8] and epilepsy surgery have increased the range of available therapeutic options.

This supplement highlights recent advances in the understanding and application of VNS. Several review articles provide a foundation for understanding VNS therapy. When VNS therapy was approved by the FDA 5 years ago, we had a limited understanding of how the treatment worked. Although our knowledge is far from complete, Henry shares recent insight and understanding of the mechanism of action of VNS therapy. After explaining the evolution of VNS therapy and discussing important aspects of the clinical trials that led to FDA approval, Schachter summarizes noteworthy findings and observations reported during the subsequent 5 years. In a review of the current status of VNS therapy in patients younger than 18 years, Wheless and Maggio note that seizure reduction and improvement in quality of life are comparable in both adult and pediatric VNS populations, suggesting that the success of VNS therapy is not dependent on age.

Other articles in this supplement share study results that may provide practical advice for physicians who treat patients with VNS. Renfroe and Wheless compared VNS patients who were implanted within 5 years of the onset of seizures or had tried four or fewer AEDs with others who were implanted more than 5 years after their seizure disorder began. Patients receiving VNS therapy earlier in their treatment course were three times more likely to report no seizures after 3 months of treatment. Determining optimal VNS device parameters for individual patients is similar to titrating AEDs. Heck et al. discuss the role of each VNS device parameter—output current, pulse duration, frequency, and duty cycle—and provide an algorithm for their adjustment to achieve seizure control. Drawing from the VNS outcome registry maintained by the device manufacturer, Labar discusses seizure rate changes of patients whose number of AEDs increased, decreased, switched, or were unchanged during their first 12 months on VNS therapy. Ben-Menachem et al. compare inpatient costs of patients with refractory seizures before and after VNS therapy. In their study, decreased costs attributed to reductions in hospitalization exceeded the major costs associated with VNS therapy. In addition, cost savings were evident even among patients whose seizure frequency was reduced by 25% or less.

Finally, two articles look toward the future of VNS therapy in treating depression and other neurological disorders. Harden provides background information on the occurrence of depression with epilepsy, including seizure types that appear to be accompanied by a greater incidence of depression. The review also discusses the effects of some AEDs on depression, some psychotropic drugs on epilepsy, and VNS therapy on both epilepsy and depression. Exploring possible future directions for VNS therapy, George et al. examine possible applications beyond refractory seizures. They outline the progress of the study of VNS therapy for patients with depression, headache, Alzheimer's disease, and obesity.

It is fitting that the publication of this supplement coincides with the fifth anniversary of the FDA's approval of VNS. The next 5 years will yield additional information for treating patients with this novel therapy.

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Therapeutic mechanisms of vagus nerve stimulation

Thomas R. Henry, MD

Article abstract—Experiments in acute and chronic animal models of epilepsy provide mechanistic insight into the acute abortive, acute prophylactic, and chronic progressive prophylactic, anti-seizure effects of vagus nerve stimulation (VNS) observed in human epilepsies, and demonstrate antiepileptogenic effects of VNS in the kindling model. Anatomic-physiologic studies, experimental epilepsy studies, and human imaging, EEG, and CSF studies suggest that multiple mechanisms underlie the antiseizure effects of VNS and that alterations of vagal parasympathetic efferent activities do not underlie these antiseizure effects. Putative antiseizure mechanisms are mediated by altered vagal afferent activities, and probably include altered activities in the reticular activating system, the central autonomic network, the limbic system, and the diffuse noradrenergic projection system. Anatomic-physiologic studies fully account for the common and rare adverse effects of VNS. Current understandings of antiepileptic drug (AED) and VNS therapeutic mechanisms strongly support the "common sense" interpretation of the clinical studies: i.e., adjunctive VNS can add antiseizure effect to any AED regimen, with no interactive toxicity and no effect on drug distribution and elimination.

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The mechanisms by which therapeutic vagus nerve stimulation (VNS) reduces seizure activity in humans and in experimental models of epilepsy were not known at the time when the United States FDA approved VNS as adjunctive therapy for partial epilepsies. Considerable progress in mechanistic VNS research has occurred over the last 5 years. Animal and human studies, the subject of this review, contribute differently to our understanding of VNS mechanisms. Mechanistic VNS research generally presumes that effects of VNS are mediated by induced action potentials in the left cervical vagus nerve. Although mechanical effects, ischemia, and other injury to the nerve might occur during device implantation, evidence of nerve injury is uncommon and it is unlikely that nerve injuries would be so consistent as to explain consistent therapeutic benefit. The anatomic distribution of vagal projections probably underlies the therapeutic actions of VNS.

Vagal pathways in the peripheral and central nervous system. *Vagus nerve composition and distribution.* The superior portions of the vagus nerves are attached by multiple rootlets to the medulla. The vagus nerves exit the skull through the jugular foramina. In the neck, each vagus nerve lies within the carotid sheath, between the carotid artery and the jugular vein (figure 1). In the upper chest, the vagi run on the right and left sides of the trachea. The complex abdominopelvic courses of each vagus earned the vagus nerve its name as the Latin term for "wanderer."

The vagus nerve carries somatic and visceral afferents and efferents. The efferent fibers mainly originate from neurons located in the medulla oblongata. The afferent fibers mainly originate from two parasympathetic ganglia located near the base of the skull.[1,2] Narrow-caliber, unmyelinated C-fibers predominate over faster-conducting, myelinated, intermediate-caliber B-fibers and thicker A-fibers in the cervical portion of the vagus nerve.[3] Vagal efferents innervate striated muscles of the pharynx and larynx as well as most of the thoracoabdominal viscera.

Afferents compose about 80% of the fibers in the cervical portion of the vagus.[4] Most of the neurons that contribute afferent fibers to the cervical vagus have cell bodies located in the superior (jugular) vagal ganglion and the larger inferior (nodose) vagal ganglion, which are located at and immediately below the jugular foramen. A larger group of special and general visceral afferents carry gustatory information, visceral sensory information, and other peripheral information. A small group of vagal somatosensory afferents carry sensory information from skin on and near the ear.

Medullary origins of vagal efferents. Most vagal efferents are parasympathetic projections to the heart, lungs, stomach and intestines, liver, pancreas,

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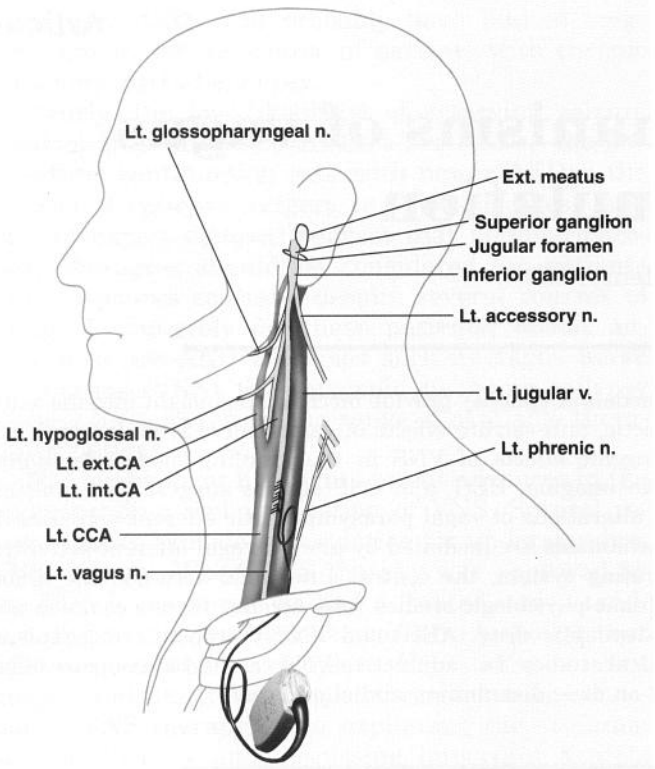

Figure 1. The cervical vagus nerve and vagus nerve stimulation. Implantation site for contacts of the leadwire on the left vagus nerve is limited to the mid-inferior cervical region, as shown schematically. The nearby phrenic nerve might mistakenly be implanted instead of the left vagus, a rarely reported and poorly tolerated complication. Lt. = left; n. = nerve; CCA = common carotid artery; CA = carotid artery; Ext. = external.

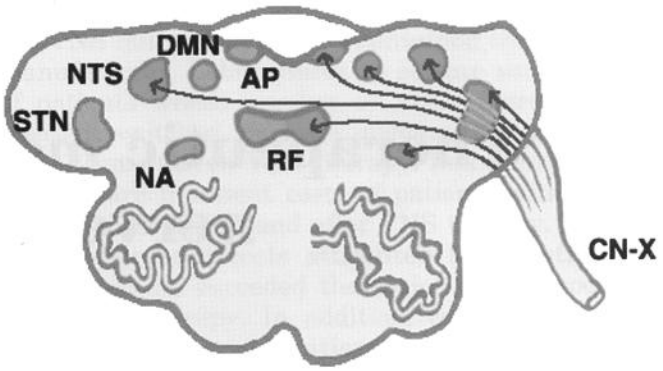

Figure 2. Schema of the dorsal medullary complex of the vagus. The left vagus nerve's afferent fibers synapse on six nuclei of the dorsal medulla ipsilaterally and also decussate to synapse on the contralateral nucleus of the tractus solitarius. Nerve terminations are indicated in blue, but most labels are placed on the homologous nucleus contralateral to the termination. NTS = nucleus of the tractus solitarius; AP = area postrema; STN = spinal trigeminal nucleus; RF = medullary reticular formation; DMN = dorsal motor nucleus of the vagus; NA = nucleus ambiguus.

and kidneys. These efferents originate from preganglionic neurons located in the dorsal motor nucleus of the vagus and in the nucleus ambiguus, in the medulla (figure 2). The vagal parasympathetic efferents synapse on neurons located in parasympathetic ganglia. These ganglia are located in or near the target organs. The two vagus nerves are asymmetric with regards to cardiac innervation. The left vagus nerve carries most of the parasympathetic fibers that less densely innervate the ventricles, and the right vagus nerve carries most of the parasympathetic fibers that more densely innervate the cardiac atria.[5] Therefore, vagal anatomy favors left (over right) vagus stimulation to avoid cardiac effects. Actual measurements of cardiac rhythm with Holter monitoring, of respiratory function with pulmonary function tests, and of gastrointestinal parasympathetic effects with serum gastrin levels show remarkably little vagal visceroeffector activity during therapeutic VNS in humans.[6-12] Most demonstrable visceroeffector alterations during therapeutic VNS in humans occur during stimulation of distal branches of the vagus,[9] during unusual states of intervention, such as general anesthesia,[12] in patients with significant medical conditions that are not directly related to their epilepsy,[11] or are measurable effects without clinical manifestations.[10] As a group, these studies raise concern over possible adverse effects of VNS that may be specific to particular nonepileptic medical conditions involving viscera that receive vagal innervation. With the exception of obstructive sleep apnea, which has been the subject of one pilot study in patients receiving VNS,[11] VNS has not been studied in series of patients with cardiac arrhythmias, congestive heart failure, or other dysfunctions of vagally innervated organs.

Each vagus nerve contains efferents that innervate the vocal cords and other skeletal muscles of the larynx and pharynx unilaterally. The α-motor neurons of these efferent axons are located in the nucleus ambiguus of the medulla. After upward titration of current output, VNS alters vocalization as the expected effect of each train of stimulation;[6,13] vocal stridor is promptly reversible with current reduction.

Medullary synapses of vagal afferents and the nucleus of the tractus solitarius. Vagal afferents traverse the brainstem in the solitary tract, terminating with synapses mainly located in nuclei of the dorsal medullary complex of the vagus.[14-16] Most vagal afferents synapse in these structures of the medulla (figure 2): (a) nucleus of the tractus solitarius (NTS); (b) nucleus of the spinal tract of the trigeminal nerve; (c) medial reticular formation of the medulla; (d) area postrema; (e) dorsal motor nucleus of the vagus; and (f) nucleus ambiguus. Among these structures, the NTS receives the greatest number of vagal afferent synapses, and each vagus nerve synapses bilaterally on the NTS. The vagal afferents carry information concerning visceral sensation (from the pharynx, larynx, trachea, and thoracoabdominal organs), somatic

sensation (from a small area of skin on and near the external ear), and taste (from receptors in the periepiglottal pharynx).

The vagal afferent synapses not only use the usual excitatory (glutamate and aspartate) and inhibitory (γ-aminobutyric acid, or GABA) transmitters but also use acetylcholine and a wide variety of neuropeptides.[17,18] As a group, these substances act very rapidly at neuronal membrane ion channels, and act more slowly via intraneuronal second messengers, such as G-proteins.

Each vagus nerve bifurcates on entering the medulla to synapse in the NTS bilaterally. The NTS extends as a tube-like structure above and below the vagal entry level, in the dorsal medulla and pons. In addition to dense innervation by the vagus nerves, the NTS also receives projections from a very wide range of peripheral and central sources,[1,2,15,19] including other peripheral nerves (the carotid sinus nerve, the aortic depressor nerve, and cranial nerves V, VII, and IX), the spinal cord (via the spinosolitary tract), multiple brainstem structures (the area postrema, the rostral ventrolateral medulla, the parabrachial nucleus of the pons, the Kölliker-Fuse nucleus, the dorsal tegmental nucleus of the midbrain, and other sites), and cerebral structures (the paraventricular nucleus and lateral and posterior regions of the hypothalamus, and the central nucleus of the amygdala). The NTS receives a wide range of somatic and visceral sensory afferents, receives a wide range of projections from other brain regions, performs extensive information processing internally, and produces motor and autonomic efferent outputs. For these reasons the NTS has been likened to a small brain within the larger brain. The vagus and associated sensory endings are the principal sensory organ of this small "brain within a brain."

Polysynaptic vagal projections to the pons, midbrain, and cerebellum. The NTS projects most densely to the parabrachial nucleus of the pons, with different portions of the NTS projecting specifically to different subnuclei of the parabrachial nucleus. The NTS projects to a wide variety of structures within the posterior fossa,[1,2,20,21] as shown schematically in figure 3, including all of the other nuclei of the dorsal medullary complex, the parabrachial nucleus and other pontine nuclei, the vermis and inferior portions of the cerebellar hemispheres, and the periaqueductal gray. Through disynaptic parabrachial relay projections, the NTS can influence activities of respiratory pattern generation and pain modulation. Alterations in respiratory pattern are not commonly observed during VNS, although patients with obstructive sleep apnea may in some cases experience increased apneas and hypopneas while asleep during high-frequency VNS.[11] The periaqueductal gray is involved in central pain processing, and local alterations in processing during VNS may underlie the antinociceptive effects of VNS in humans.[22] Through its own monosynaptic projections, the NTS can directly influence activities of parasympathetic and sympathetic effector neurons, cranial nerve α-motor neurons, motor systems subserving posture and coordination, ascending visceral and somatic sensory pathways, and the local arousal system.

Ponto-Cerebellar Projections of NTS

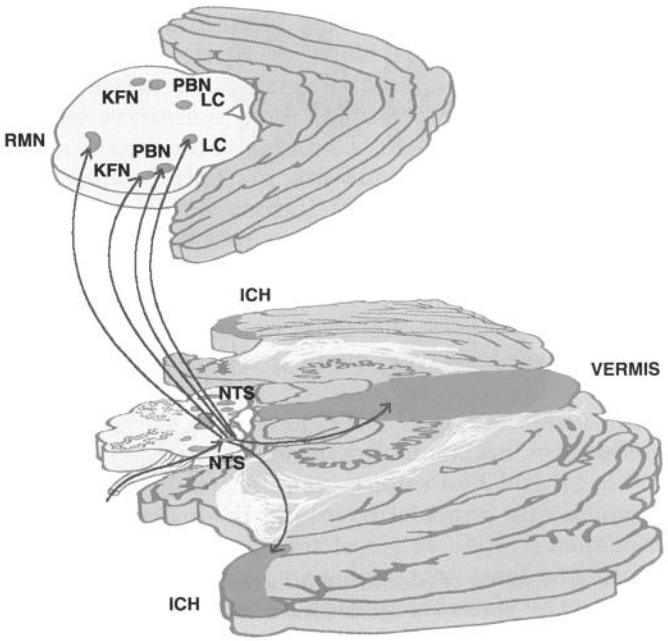

Figure 3. Schema of the bulbo-cerebellar polysynaptic projections of the nucleus of the tractus solitarius. The left vagus nerve projects densely upon the NTS bilaterally, and the NTS projects to inferior and medial cerebellar regions, and to multiple pontine and mesencephalic nuclei. NTS = nucleus of the tractus solitarius; ICH = inferior cerebellar hemisphere; KFN = Kölliker-Fuse nucleus; LC = locus coeruleus; RMN = raphe magnus nucleus; PBN = parabrachial nucleus.

Vagal afferents project to the noradrenergic and serotonergic neuromodulatory systems of the brain and spinal cord via the NTS.[23] The locus coeruleus, a pontine nucleus, provides extremely widespread noradrenergic innervation of the entire cortex, diencephalon, and many other brain structures. The NTS projects to the locus coeruleus through two disynaptic pathways, an excitatory pathway via the nucleus paragigantocellularis and an inhibitory pathway via the nucleus prepositus hypoglossi.[24] Therefore, VNS effects on the locus coeruleus may be excitatory, inhibitory, or neutral. Unlike the relatively compact locus coeruleus, the raphe nuclei are distributed among midline reticular neurons from the inferior medulla through the mesencephalon. The raphe nuclei provide extremely widespread serotonergic innervation of the entire cortex, diencephalon, and other brain structures. The NTS projects to multiple raphe nuclei, as do other nuclei of the dorsal medullary vagal complex, but the complexity of NTS-raphe pathways and transmitters is greater than for NTS-locus coeruleus interactions.[1,2] The locus coeruleus is the major source of norepinephrine and the raphe of

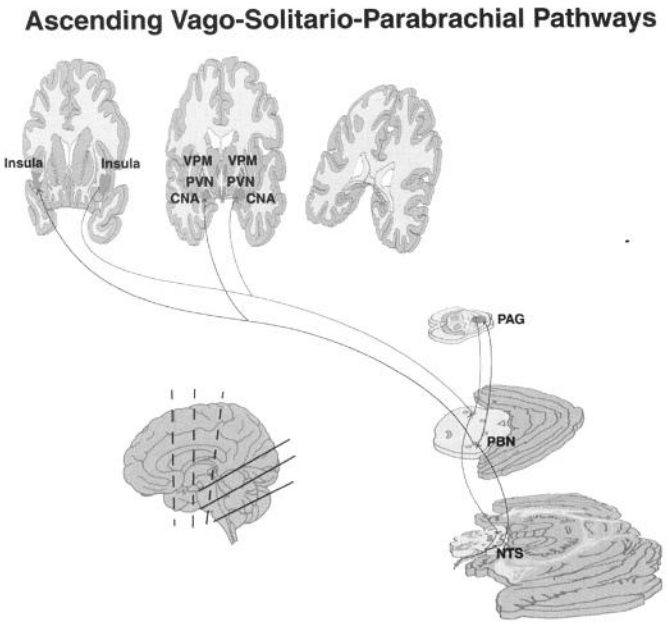

Figure 4. Schema of ascending bilateral vago-solitario-parabrachial pathways of the central autonomic, reticular activating, and limbic systems. Left vagal-bilateral NTS projections, through synapses in the parabrachial nuclei, provide dense innervation of autonomic, reticular, and limbic forebrain structures, as shown. Additional, more direct NTS projections to the forebrain, and other polysynaptic pathways, are discussed in the text. NTS = nucleus of the tractus solitarius; PBN = parabrachial nucleus; PAG = periaqueductal gray; CNA = central nucleus of the amygdala; PVN = periventricular nucleus of the hypothalamus; VPM = ventral posteromedial nucleus of the thalamus.

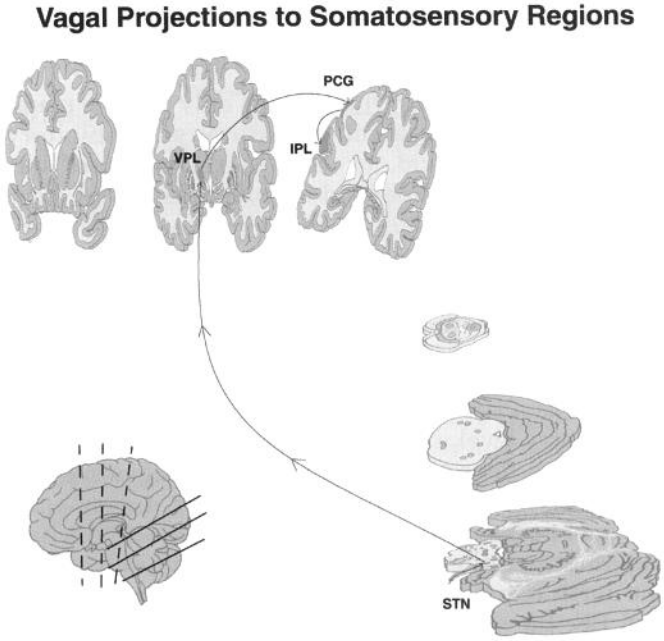

Figure 5. Schema of the ascending unilateral vago-trigemino-thalamocortical pathways of the somatosensory system. Left vagal projections to the left spinal trigeminal nucleus subserve conscious sensation of deep pharyngeal tissues and other modalities, as discussed in the text. STN = spinal trigeminal nucleus; VPL = ventral posterolateral nucleus of the thalamus; PCG = post-central gyrus; IPL = inferior parietal lobule.

serotonin in most of the brain. Vagal-locus coeruleus and vagal-raphe interactions are potentially relevant to VNS mechanisms because norepinephrine, epinephrine, and serotonin exert antiseizure effects, among other actions.[25-28]

The area postrema also receives afferent synapses from the vagus nerve, from several other peripheral nerves, and from central autonomic structures. The area postrema projects densely to the NTS and to the parabrachial nucleus, and less densely to the dorsal motor nucleus of the vagus, the nucleus ambiguus, and several other sites. The area postrema coordinates the vomiting reflex and participates in cardiovascular, renovascular, and respiratory reflexes. The area postrema functions as an autonomic nucleus at the blood-brain interface, as one of the circumventricular organs.

Polysynaptic vagal projections to cerebral structures. The vagus nerve afferents have some disynaptic projections to the thalamus and hypothalamus (via the NTS and the spinal trigeminal nucleus). Most of the widespread vagal projections to cerebral structures traverse three or more synapses (figures 4 and 5).

The spinal trigeminal nucleus projects unilaterally to somatosensory thalamic neurons, which project to the inferior postcentral gyrus and inferior parietal lobule.[2] Vago-trigemino-thalamocortical processing mediates conscious laryngeal and pharyngeal sensation. Predictably, increasing VNS output current can cause uncomfortable sensations, which are rapidly reversible with current reduction.

The NTS projects to several structures in the cerebral hemispheres,[1,2] including hypothalamic nuclei (the periventricular nucleus, lateral hypothalamic area, and other nuclei), thalamic nuclei (including the ventral posteromedial nucleus, paraventricular nucleus, and other nuclei), the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the nucleus accumbens. Through these projections the NTS can directly influence activities of extrapyramidal motor systems, ascending visceral sensory pathways, and higher autonomic systems. Through its projection to the amygdala, the NTS gains access to amygdala-hippocampus-entorhinal cortex of the limbic system, which are the sites that most often generate complex partial seizures.

The vagus-NTS-parabrachial pathways support additional higher cerebral influences of vagal afferents. The parabrachial nucleus projects to several structures within the cerebral hemispheres,[2,29] including the hypothalamus (particularly the lateral hypothalamic area), the thalamus (particularly intralaminar nuclei and the parvicellular portion of the ventral posteromedial nucleus), the amygdala (particularly the central nucleus of the amygdala, but also basolateral and other amygdalar nuclei), the anterior insula, and infralimbic cortex, lateral prefrontal cortex, and other cortical regions. The ante-

rior insula constitutes the primary gustatory cortex. Higher-order projections of the anterior insula are particularly dense in inferior and inferolateral frontal cortex of the limbic system. The parabrachial nuclei function as major autonomic relay and processing sites for gustatory, pulmonary, and other autonomic information. Altered vagal sensory inputs to these systems may account for the occasional patient who experiences subjective dyspnea during VNS, which consistently occurs in the absence of objective changes in pulmonary function.[7]

The medial reticular formation of the medulla receives afferent projections from the vagus nerve and from many other sources. The medial reticular formation of the medulla projects to the nucleus reticularis thalami (a thalamic nucleus that projects to most of the other thalamic nuclei and exerts strong influences on synchronization of thalamocortical projections) and to the intralaminar nuclei of the thalamus (the centromedian and other thalamic nuclei that have extremely widespread projections to cerebral cortex and the striatum).[1,2,29,30] The reticular formation coordinates a variety of activities (including generation of sleep spindles and slow EEG waves of sleep via diffuse thalamocortical projections) with diffuse projections to cerebral structures, as well as descending projections.[31-33] Patients often report improved alertness during VNS. A study of patients without sleep disorders revealed improved diurnal alertness during VNS, which was independent of seizure reductions.[34] Improved reticular activating system function must mediate improved alertness, although the mechanisms of VNS alterations in arousal are unclear.

Mechanistic studies in animal models of epilepsy. *The initial hypothesis of VNS anti-seizure effects.* Dr. Jacob Zabara[35] first proposed that VNS might antagonize seizures by desynchronizing electrocerebral activities. Early neurophysiologic studies found that VNS can induce EEG desynchronization in cats.[36] Hypersynchronized cortical and thalamocortical neuronal interactions characterize seizures in animal models of partial and generalized epilepsies, and ictal hypersynchrony among cerebral regions characterizes human intracranial electrophysiology.[37-39] Zabara postulated that desynchronizing these hypersynchronous activities would confer antiseizure effects on VNS. Empirical observations in animal models of epilepsy subsequently demonstrated anti-seizure effects of VNS.

General effects of VNS on brain function. Anesthetized cats demonstrated EEG desynchronization during VNS in the earliest experiment.[36] Later studies showed that VNS also can induce increased EEG synchronization and can decrease interictal epileptiform EEG discharges in animals, depending on the frequency of stimulation.[40-42] Intermittent VNS reduced or abolished interictal epileptiform activities that were induced by focal cortical application of strychnine[42] or penicillin.[41]

The vagus nerves contain A-, B-, and C-fibers as histopathologically defined by diameter and myelination.[3,43] The vagal A-fibers (the largest and most heavily myelinated fibers) have the lowest amplitude-duration threshold required for VNS to excite action potentials, with higher thresholds for B-fiber excitation, and highest thresholds to excite the narrow, unmyelinated C-fibers.[43] These studies also showed that, in anesthetized rats, effects on heart rate (bradycardia) and respiration (apnea or hypopnea) occurred only at VNS thresholds sufficient to excite action potentials in C-fibers.[43] The almost complete absence of parasympathetic visceral effects during human VNS and other indirect evidence[14] suggest that C-fibers are not activated during therapeutic VNS.

Behavioral effects of VNS have not been fully studied in animals (or in humans). An interesting pair of rodent and human studies by Clark et al.[44,45] showed evidence of improved learning and memory during clinically relevant levels of VNS. A footshock avoidance task was learned by rats implanted with vagus nerve electrodes, and immediately after training rats received either VNS or sham stimulation. The rats that received VNS retained the task performance significantly better after 24 hours than did the control group. Performance improvements were associated more with intermediate than with highest or lowest amplitudes of VNS in these studies.[45]

Chemically induced tremors were suppressed during left cervical VNS in the rodent harmaline tremor model.[46] The mechanisms by which VNS might suppress tremor remain unclear.

Naritoku et al.[47] reported that VNS was able to increase activity in known vagal projection pathways, as measured by neuronal *fos* expression. Rats received VNS for 3 hours before sacrifice and immunomapping of *fos*, a neuronal nuclear protein that has increased concentrations at sites of increased overall biochemical activity. Control groups either did not receive any electrical stimulation or received electrical stimulation of tissues near but not in the vagus nerve. Intermittent VNS caused acute increases in neuronal *fos* expression in the medullary vagal complex, the locus coeruleus, several thalamic and hypothalamic nuclei, the amygdala, and the cingulate and retrosplenial cortex compared with the control group *fos* distributions.[47]

Anti-seizure properties of VNS. Animal studies established that the antiseizure effects of VNS have three distinct temporal patterns: (a) acute abortive effects, in which an ongoing seizure is attenuated by VNS applied after seizure onset; (b) acute prophylactic effects, in which seizure-inducing insults are less effective in provoking seizures when applied within minutes after the end of a train of VNS than these insults would be in the absence of VNS or at longer periods after VNS; and (c) chronic progressive prophylactic effects, in which total seizure counts (totaled continuously over long periods between and during intermittent VNS) are reduced more after

chronic stimulation over weeks or months than after acute stimulation over less than a day. Animal studies also showed that VNS can antagonize the development of epilepsy in the kindling model of epileptogenesis.

Seizures were prevented or attenuated by VNS in several experimental models of acute symptomatic seizures in rats, dogs, and monkeys. These studies used maximal electroshocks to the head and the systemic proconvulsants pentylenetetrazol and strychnine to induce seizures.[41,43,48,49] These are the same acute insults most often used to screen potential AEDs for antiseizure efficacy. These studies consistently showed that, after a seizure began, it could be stopped or attenuated with application of VNS during the seizure.

The VNS studies in these acute epilepsy models also demonstrated that antiseizure effects of VNS outlast the period during which the nerve is stimulated. Takaya et al.[48] examined the temporal profile of post-stimulation seizure antagonism in detail. In rats with seizures induced by pentylenetetrazol, which was administered at various intervals after the end of a train of VNS, they found anticonvulsant effects that declined gradually over 10 minutes after VNS. They also noted a chronic prophylactic effect, in that greater anticonvulsant effects occurred after longer, cumulative periods of intermittent VNS. Together, these acute studies showed that the antiseizure effects of VNS were greater at frequencies of stimulation above 10 Hz and below 60 Hz for both acute abortive and acute prophylactic effects.

A chronic model of neocortical epilepsy provided further evidence of the antiseizure effects of VNS,[50] in that VNS abolished or reduced seizures due to topical instillation of cobalt on neocortex in primates. Unlike VNS in subprimate models of epilepsy, this study did not find that VNS reduced interictal spikes despite antiseizure effects in these monkeys.[50] These primate studies showed both acute and chronic prophylactic effects of VNS. More recently, a study of VNS in a chronic model of temporal lobe epilepsy also showed antiseizure effects of VNS,[51] in that amygdala kindling in cats was markedly reduced by pretreatment with VNS.

Peripheral, efferent vagal effects do not mediate antiseizure actions of VNS, based on two critical mechanistic experiments. Zabara et al.[49] induced motor seizures in dogs using systemic boluses of strychnine or pentylenetetrazol. Acute application of VNS terminated these seizures. Antiseizure VNS effects were not reversed by transection of the vagus nerve distally to the site of vagal stimulation. Krahl et al.[52] chemically lesioned the vagal efferents just distal to the site of cervical stimulation in rats. This study was based on the observation that essentially all vagal efferents below the cervical stimulation site are C-fibers. Capsaicin was used to chemically destroy the C-fibers without affecting larger myelinated (afferent) vagal fibers. Systemic pentylenetetrazol induced seizures in lesion and control groups, and then VNS was used to attenuate the pentylenetetrazol-induced seizure. VNS attenuated seizures equally well, whether or not vagal C-fibers had been destroyed.[52]

A mechanistic role for the locus coeruleus in VNS antiseizure effects was shown in the rodent maximal electroshock model.[53] Lidocaine infusion (to cause local anesthesia acutely) and 6-hydroxydopamine infusion (to cause norepinephrine depletion chronically) into the locus coeruleus bilaterally were each shown to fully reverse the antiseizure effects of VNS.[53] Similar studies of other sites in the vagal projection pathways have not been reported, nor have mechanistic studies using chronic experimental models that are more similar to human epilepsies. Nevertheless, the locus coeruleus and noradrenergic actions must be primary targets of future mechanistic studies of VNS.

The importance of the NTS in regulating epileptic excitability was demonstrated in a recent study of Walker et al.[54] Various means of inhibiting NTS output, including manipulations of both GABA and glutamate neurotransmission in the NTS, were shown to reduce susceptibility of rats to seizure induction by systemic pentylenetetrazol, by systemic bicuculline, or by focal infusion of bicuculline into the area tempestas. On the basis of this functional study and the extensive investigations of vagal afferent pathways, it seems clear that the NTS must transmit and modulate VNS antiseizure actions.

Mechanistic studies in human epilepsies. *Electrophysiological studies of VNS in humans.* Electroencephalography. The earliest theorized antiseizure mechanism was that VNS desynchronizes the human EEG so as to interfere with maintenance of the hypersynchronous state of partial and generalized seizures. This theory is consistent with observations of desynchronization of the EEG in some animal experiments.[40,42]

The human EEG has been observed during VNS by four groups. The University of Florida group studied nine partial epilepsy patients at periods before and after chronic VNS.[55] Normal EEG activities (including normal hyperventilation-induced slowing) were not altered during epochs of VNS and had not changed during nonstimulation periods after chronic VNS (compared with pre-VNS baseline EEG), either on visual interpretation or on quantitative frequency analysis of the EEG. Two patients, who had long runs of interictal epileptiform activity, had no change in spiking during epochs of VNS or during nonstimulation periods after chronic VNS. Other patients with only occasional interictal epileptiform activity also had no change in spiking during nonstimulation periods after chronic VNS. Two patients were able to abort behavioral seizures when the stimulator was activated manually during early periods of the events, and in both cases the EEG manifestations of the seizures also appeared to be terminated during VNS.

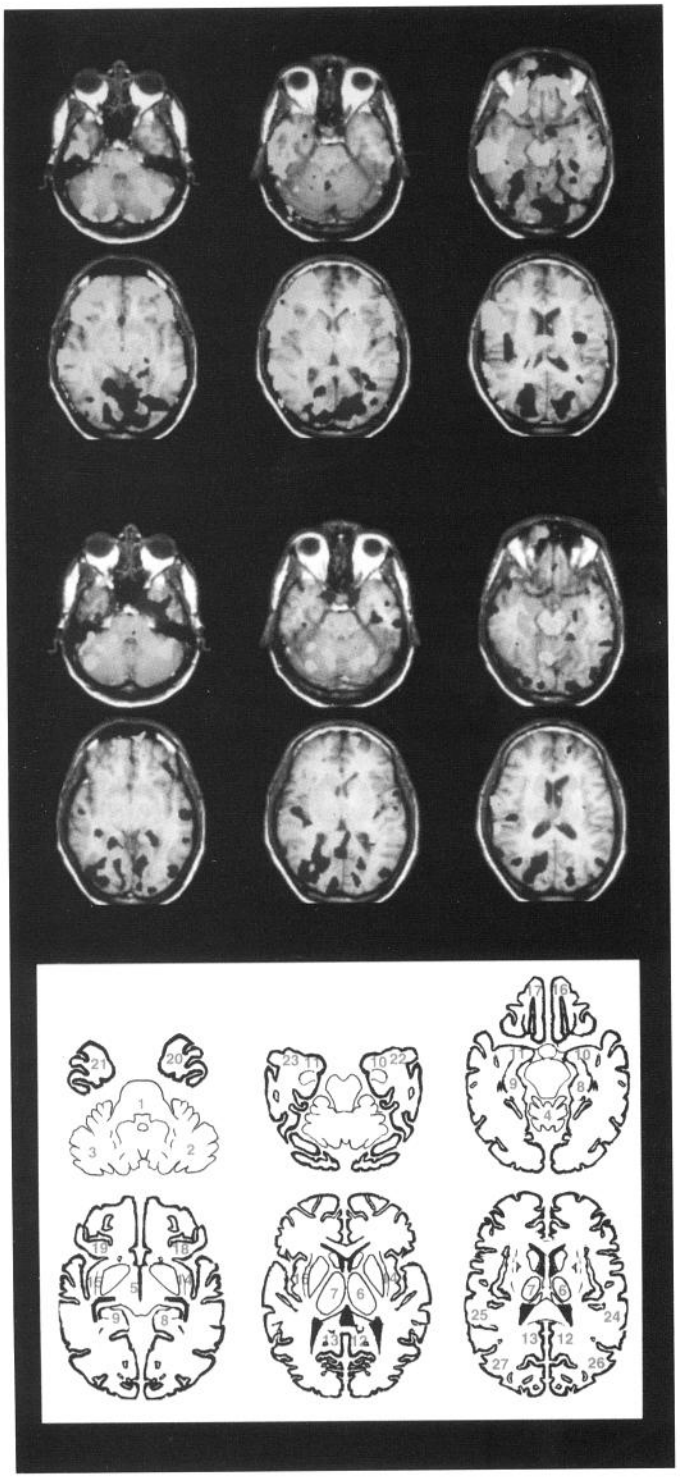

Figure 6. Activation [^{15}O]-H_2O PET studies of acute vagus nerve stimulation. Data were obtained first with the stimulator shut off, then during VNS, within the first day after chronic VNS began (using techniques described in reference 62). Volumes of blood flow increases (in yellow) and decreases (in blue), which have T-values of 5 or greater, are superimposed on gray-scale magnetic resonance images. The subjects' left is displayed on image right. The first two rows consist of axial images with approximately 1-cm spacing, arranged from inferior (upper left) to superior (lower right), of the high-stimulation group (n = 5). The middle two rows are similarly arranged data for the low-stimulation group (n = 5). The bottom two rows are axial brain schemata at the same levels as for the other rows, with numbers inserted to indicate the locations of these structures: 1 = dorsal-rostral medulla; 2/3 = left/right inf. cerebellar hemisphere; 4 ≐ cerebellar vermis; 5 = hypothalamus; 6/7 = left/right thalamus; 8/9 = left/right hippocampus; 10/11 = left/right amygdala; 12/13 = left/right cingulate gyrus; 14/15 = left/right insula; 16/17 = left/right orbitofrontal cortex; 18/19 = left/right inf. frontal gyrus; 20/21 = left/right entorhinal cortex; 22/23 = left/right temporal pole; 24/25 = left/right inf. postcentral gyrus; 26/27 = left/right inferior parietal lobule. From reference 69, with permission.

Salinsky and Burchiel[56] studied quantitative scalp EEG measures in six partial epilepsy patients after more than 6 months of chronic VNS. Acquisition of EEG occurred during maximal arousal. Series of EEG acquisition consisted of three epochs lasting 60 seconds each, recorded sequentially just before a train of VNS, during VNS, and just after VNS. Visual interpretation of the EEGs during the baseline, activation, and post-activation conditions did not show any changes across these conditions in any individual. Quantitative frequency analysis of activities at each of the standard 10–20 system electrodes did not show significant differences in total power across these conditions in any individual. Even with averaging of quantified data across the entire group, no significant differences by condition were shown for total power, median frequency, or power in any of the standard frequency bands. Therefore, although these two groups studied EEG effects of VNS with rather different paradigms, neither showed significant quantitative effects of VNS on the human EEG.

One patient undergoing presurgical evaluation with intrahippocampal electrodes showed effects of VNS on baseline frequency of interictal epileptiform discharges.[57] The hippocampal spikes decreased during VNS at 30 Hz but increased over baseline during VNS at 5 Hz.

Reductions in interictal epileptiform activity during chronic VNS also were reported by Koo.[58] This group studied a population with quite different characteristics from those of the two earlier series, including (a) patients with generalized onset and partial onset seizures, (b) patients with greater frequency of interictal discharges, and (c) younger patients. In this group, both generalized and focal spikes were diminished during 12 months of VNS therapy. Spikes were manually counted, without computerized spike detection or automated analyses of background EEG activities. Spike reduction did not correlate well with seizure reduction. Therefore, this study provided indirect evidence of VNS interference with hypersynchronous, thalamocortically mediated spike generation but did not show definite relevance of this action to seizure reduction.

Evoked potentials. Vagus evoked potentials were studied by two groups with rather different results.[59,60] Hammond et al.[59] used scalp electrodes to record a single surface-negative potential of high am-

plitude with a peak at about 12 milliseconds from stimulus onset and a very widespread field. Topographic mapping over craniocervical regions revealed that the vagus evoked potential had a maximum over the left cervical region. The generators were shown to be left anterior cervical skeletal muscles by abolishing the vagus evoked potential with a neuromuscular blocking agent, and then showing return of the vagus evoked potentials after effects of neuromuscular blockade were reversed. Tougas et al.[60] recorded a series of three surface-negative potentials at about 71, 194, and 328 milliseconds from stimulus onset, also using scalp electrodes. Similar results were obtained on electrical stimulation of the esophagus, with slightly longer latencies to all three surface-negative peaks in epileptic than in healthy subjects (attributed by the investigators to effects of AEDs in slowing neural conduction). In many respects the techniques used to record vagus evoked potentials were similar in both investigations, but the amplitude of vagal stimulation was 14 mA in one study[60] and 3.5 mA or lower in the other study.[59]

The effects of acute and chronic VNS on other evoked potentials also have been studied.[59,61] In three patients, Naritoku et al.[61] found no effects of chronic VNS on brainstem auditory evoked potentials but did find some prolongation of the latency from the N13 to N20 peaks (often considered to represent central projections to thalamocortical areas) of median nerve somatosensory evoked potentials. However, in nine patients, Hammond et al.[59] found no effects of acute or chronic VNS on visual, somatosensory, brainstem auditory, 40-Hz auditory, or P300 auditory ("cognitive") evoked potentials. Both groups used similar techniques to record median nerve somatosensory evoked potentials, and it is therefore difficult to explain their divergent results.

Cerebral blood flow studies of VNS in humans. Noninvasive imaging of synaptic activity can be performed with PET in humans. Rapidly occurring changes in regional brain blood flow are considered to reflect primarily changes in transsynaptic neurotransmission in the absence of seizures, arterial thromboembolism, and other brain vascular dysfunctions.[62] Such alterations in regional cerebral blood flow (CBF) are observed during specific motor, sensory, or cognitive processing in humans, as shown by many PET studies that compare regional distributions of $[^{15}O]$-H_2O with and without particular tasks and stimuli.[63-67] These PET studies have shown highly focal postcentral and opercular regions that have increased CBF during focal somatosensory stimulation.[64-66] Visceral sensory activation PET studies demonstrated increased $[^{15}O]$-H_2O activity bilaterally in the thalami and in the pre- and postcentral gyri during intrarectal balloon dilation.[68] PET imaging of CBF during VNS can therefore be used to look for brain regions that significantly change levels of synaptic activity during VNS.

Changes in CBF induced by acute VNS. Acute effects of VNS on regional brain blood flow were studied in 10 patients who underwent PET scans before receiving VNS and again within 20 hours after VNS was initiated.[69] Parameters for VNS were at high levels for five patients and low levels for five patients. Statistical testing analyzed the differences between the baseline scans and the VNS activation scans, both within individuals and also in groups of patients. In both the high- and the low-stimulation groups, VNS induced significant blood flow increases in the dorsal-central-rostral medulla (figure 6), which is the site of the dorsal medullary vagal complex (the nucleus of the tractus solitarius, the nucleus of the spinal tract of the trigeminal nerve, the nucleus ambiguus, and the dorsal motor nucleus of the vagus). The high-stimulation group had larger volumes of activation (increased CBF during VNS) and deactivation (decreased CBF during VNS compared with baseline CBF) sites over both cerebral hemispheres than did the low-stimulation group.[69] In both groups, regional blood flow changes during acute VNS demonstrated sites of increased synaptic activity in the right thalamus and right postcentral gyrus (the "sensory strip"), which are the major sites of cerebral processing of left-sided somatic sensation. This is not surprising because all of the patients reported feeling the left cervical tingling sensations that normally occur during VNS. However, most of the cortical and subcortical regions that had altered blood flow during VNS are not involved in sensory processing. Both high- and low-stimulation groups had VNS-activated sites in the inferior cerebellar hemispheres bilaterally.

Significant VNS-induced blood flow alterations were observed bilaterally in supratentorial structures of the autonomic and limbic systems. Significant blood flow increases occurred in the hypothalami and in the left and right anterior insular cortices in both groups. The high-stimulation group had significant blood flow increases in the left and right orbitofrontal gyri, right entorhinal cortex, and the right temporal pole, which did not occur in the low-stimulation group. Both groups had significant decreases in amygdalar, hippocampal, and posterior cingulate gyral blood flow, which were bilateral in each case. It is of some interest that the amygdala and hippocampus had bilaterally reduced synaptic activity during VNS, because these regions often are involved early in complex partial seizures. Perhaps regions of VNS-induced synaptic activity decreases have a lower probability of sustaining repetitive ictal firing simply as a passive effect of decreased excitatory synaptic activity.

Bilateral thalamic increases in blood flow occurred in both high- and low-stimulation groups during VNS. Many thalamic nuclei contain thalamocortical relay neurons which, as a group, project to all cortical areas and essentially all subcortical structures.[32] Normal activities of "specific" thalamocortical relay neurons transmit pre-processed sensory information to higher levels and pre-processed motor commands to lower levels. Both "specific" and "nonspecific"

thalamocortical relay neurons drive the entire cortex through the various waking and sleep states and synchronize cortical electrical rhythms, among many other thalamic processes that initiate or modulate cortical activities.[33,39] It is reasonable to examine the thalami as regions that might generate active processes to prevent seizure onset, or to terminate or limit propagation of electrocortical seizure activities. In fact, bilateral thalamic CBF increases during acute VNS are correlated with the individual's responsiveness to chronic VNS.[70] Among the 10 patients who underwent acute VNS activation PET studies, individuals had improvements in seizure frequency ranging from 0% to 71% during 3 months of chronic VNS. Each individual had statistical analysis of his or her own PET data (*intra*subject activation analyses), and VNS-induced activations of brain regions were compared with subsequent changes in frequency of complex partial and secondarily generalized seizures. Although many cerebral regions showed significant changes in CBF during VNS, only the right and left thalami showed significant associations of CBF change with seizure responsiveness. Increased CBF in the thalami correlated with decreased seizures ($p < 0.01$). This suggests that therapeutic VNS may decrease seizures by actions that increase synaptic activities in the thalami bilaterally. Future studies will be required to determine precisely how this occurs.

Vonck et al.[71] studied immediate post-stimulation effects of acute VNS on regional CBF, using a very different protocol and generating findings very different from those of the acute VNS activation PET studies. These investigators used paired ^{99m}Tc-ethyl cysteinate dimer and SPECT scans in each subject, with one scan at baseline before VNS began and the other within an hour later, with radioligand injection just at the end of the first train of VNS. The current intensity averaged less in the SPECT study than in the PET study, and the PET study had a longer duration of VNS (intermittently over less than 1 day) before the VNS-activated scans were obtained. The SPECT study found significantly decreased left thalamic and left parietal CBF on VNS-activated scans. The PET and SPECT imaging techniques are themselves quite different, which may account for some of the observed differences. Nevertheless, it can be speculated that during VNS the thalami and other regions have increased CBF and that immediately after VNS these regions have decreased CBF compared with baseline.

Presumably functional MRI (fMRI) might be used to study in detail the time course of regional CBF alteration during VNS. Data with fMRI during VNS have been obtained in depressed patients who do not have seizures.[72] No such papers in epilepsy have been published to date, however.

Changes in CBF induced by chronic VNS. Three CBF PET studies examined patients after months or years of intermittent VNS and presumably reflect chronic effects of VNS that have been altered by brain adaptation to ongoing stimulation of the left vagus nerve.[73-75] Garnett et al.[73] reported that left VNS activated blood flow in the left thalamus and left anterior cingulate gyrus on averaged PET data of five patients. In this study, two of five patients had seizures during image acquisition. The results of this VNS activation–PET study are rendered more difficult to interpret by the inclusion of ictal scans because partial-onset seizures are known to cause complex multiregional alterations in CBF.[76] Ko et al.[75] reported that left VNS activated blood flow in the right thalamus, right posterior temporal cortex, left putamen, and left inferior cerebellum on averaged PET data from three patients. These results may have been influenced by prior epilepsy surgery, with right anterior temporal lobectomy in one case and left frontal resection in another of the three subjects.

The Emory group performed chronic VNS activation PET studies on the same 10 volunteers who underwent acute VNS activation PET, as discussed above. After 3 months of chronic intermittent VNS, each patient again had three control scans without VNS and three scans during 30 seconds of VNS.[74] Data were analyzed in the same fashion as for the acute VNS activation studies. In general, the high- and low-stimulation groups both had smaller volumes of significant activations during the chronic studies than they did during the acute studies. During acute and chronic studies, VNS-induced CBF increases had the same distributions over the right postcentral gyrus and bilateral thalami, hypothalami, inferior cerebellar hemispheres, and inferior parietal lobules. During acute studies, VNS decreased bilateral hippocampal, amygdalar, and cingulate CBF, and increased bilateral insular CBF. These regions had no significant VNS-induced CBF changes during the chronic study. (Mean seizure frequency decrease was 38% between the acute and chronic PET studies.) Thus, seizure control improved during a period over which some acute VNS-induced CBF changes declined (mainly over cortical regions) whereas other VNS-induced CBF changes persisted (mainly over subcortical regions).

Although there are several possible explanations for the differences between findings of the acute and chronic VNS activation PET studies, it is reasonable to suspect that differences between acute and chronic VNS activation PET studies may reflect brain adaptation to chronic stimulation of the left vagus nerve. Therapeutic VNS has been observed to gradually improve seizure control over periods of greater than 3 months (and in some cases over periods of greater than 1 year), even when VNS parameters are not modified over the period of improvement in seizure frequency.[77,78] Further study will be required to determine why the acute effects of VNS on brain blood flow differ from VNS effects after months or years of stimulation. Intrasubject differences between acute and chronic VNS activation scans may reveal processes of adaptation to chronic VNS, and

some of these processes may have an antiepileptic effect.

Cerebrospinal fluid studies of VNS in humans. Chronic VNS causes changes in CSF amino acid and phospholipid content, which may reflect neurochemical changes that are responsible for the antiepileptic action of VNS.[79,80] Both reports indicated similar results, with a larger patient group and longer follow-up of efficacy in the later report. Ben-Menachem et al.[80] studied CSF changes before and after 3 months of therapeutic VNS in groups receiving high versus low stimulation levels, and studied the same groups again 6 months later, after all 16 subjects received high levels of VNS.[79] Subjects were analyzed by levels of stimulation and by responsiveness of their seizures to VNS therapy. Overall, CSF concentrations of total and free GABA increased significantly in all patients at 3 months, with greater increases in the group with lower stimulation (at 3 months) and greater increases in the nonresponders (at 9 months). The entire patient group had decreased CSF concentrations of the excitatory amino acids glutamate and aspartate at 9 months, and increased CSF concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), but these changes did not reach statistical significance at 3 or 9 months. The relationship of these findings to the mechanism of the antiepileptic action of VNS is uncertain, owing in part to the fact that nonresponders had greater excitatory amino acid decreases and nonresponders had greater GABA and 5-HIAA increases than did the subjects whose seizures responded most to chronic VNS. Therefore, although these changes in CSF amino acids probably reflect actions of chronic VNS on neurotransmitter release, it is not clear that these actions are antiepileptic. On the other hand, significant CSF increases in the cell membrane phospholipid precursor ethanolamine were greatest in the high-stimulation group (at 3 months) and in the responders (at 3 and 9 months). The authors suggest that increased CSF ethanolamine levels may be a sign of increased turnover of neuronal membrane components.[79] It remains unclear how increased neuronal membrane synthesis might relate to improved seizure control.

Putative mechanisms of AEDs and of VNS in human epilepsies. The desired anti-seizure actions of VNS may be mediated (a) through increased synaptic activities in the thalamus and thalamocortical projection pathways bilaterally, leading to increased arousal and possibly to decreased synchrony of synaptic activities between and within cortical regions, (b) through intermittently increased synaptic activities in the insula, hypothalamus, and other components of the central autonomic system, (c) through transiently decreased synaptic activities in the amygdala, hippocampus, and other components of the limbic system, or (d) through intermittently increased release of norepinephrine (and perhaps also of serotonin) over widespread cerebral regions. In contrast, the major antiseizure actions of AEDs include (a) limitation of the maximal ictal rates of sustained repetitive firing of neuronal action potentials, by decreasing conductance at voltage-sensitive sodium ionophores, (b) inhibitory hyperpolarization of postsynaptic neuronal membranes, by prolonging the duration of openings or increasing the frequency of openings of the chloride ionophores that are linked with $GABA_A$ receptors so as to increase overall chloride conductance, and (c) reduction of hypersynchronous cortical spike-wave discharges, by reducing low-threshold (T-type) calcium currents of thalamocortical relay neurons.[81] It is unlikely that VNS would reduce cortical hypersynchrony by direct effects on calcium channel conductance in membranes of thalamocortical relay neurons, similar to the effects of ethosuximide and other antiabsence agents. It is likely that altered polysynaptic activities of the vago-solitario-parabrachial pathways mediate altered activities of thalamocortical relay neurons during VNS, and that antiabsence agents do not have such actions. Although some AEDs may exert adrenergic agonism, it is not clear that any AEDs use adrenergic agonism as the predominant antiseizure action. Therefore, the antiseizure effects of VNS and of AEDs appear to be largely distinct.

The mechanisms of toxicity and adverse effects also differ significantly between VNS and commonly used AEDs, as do the empirically observed occurrences of adverse effects. For example, sedative effects and impaired cognition are commonly observed with use of AEDs that increase GABAergic inhibition or that reduce rapid, repeated interneuronal action potentials by limiting sodium conductance. These adverse effects are rarely if ever attributable to VNS. Stridor of vocalization often occurs during activation of vagal efferents to the left vocal cord by VNS, but not by AED effects. Further, complex pharmacokinetic interactions among AEDs and other pharmacologic agents appear entirely unaffected by VNS. Current understandings of therapeutic mechanisms strongly support the "common sense" interpretation of the clinical studies: adjunctive VNS can add antiseizure effect to any AED regimen, with no interactive toxicity, and no effect on drug distribution and elimination.

Summary. No single mechanism of action has been shown to mediate the antiseizure effects of VNS. Anatomical pathways provide the left cervical vagus afferent and efferent fibers with access to (a) parasympathetic control of the heart and multiple other visceral organs, (b) pharyngeal muscles of vocalization, (c) a limited somatosensory representation of the head and neck, and (d) a widespread array of autonomic, reticular, and limbic structures of the brainstem and both hemispheres. Therapeutic VNS appears to have remarkably little affect on the vagal parasympathetic visceroeffectors. The common reversible adverse effects of VNS mainly involve vocalization and somatic sensation. Experimental and human studies most strongly support altered activi-

ties of the reticular activating system, the central autonomic network, the limbic system, and the diffuse noradrenergic projection system as modalities of seizure antagonism.

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Vagus nerve stimulation therapy summary

Five years after FDA approval

Steven C. Schachter, MD

Article abstract—With more than 16,000 patients implanted with the vagus nerve stimulation (VNS) therapy system (Cyberonics, Inc., Houston, Texas), VNS therapy has assumed an increasingly important role in the treatment of medically refractory seizures since its approval 5 years ago by the United States FDA. This review discusses the clinical trials that provided evidence for the approval, long-term efficacy, efficacy in special populations and co-morbid conditions, and safety and tolerability. Additional studies are suggested to further explore the capabilities of VNS therapy.

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Recent advances in antiepileptic drug (AED) therapy have provided additional options for physicians who treat patients with seizures. For patients with pharmacoresistant seizures or unacceptable side effects from AEDs, generally accepted nonpharmacologic treatments are limited to the ketogenic diet, epilepsy surgery,[1] and vagus nerve stimulation (VNS) therapy. The ketogenic diet may not be effective in adults, and a considerable proportion of patients with pharmacoresistant partial-onset seizures are not candidates for or are opposed to intracranial surgery. For such patients, VNS therapy may be a therapeutic option (figure 1). VNS was approved by the FDA in 1997 "for use 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."[2] The VNS therapy system is also approved in many European countries and Canada. Clinical experience over the past 5 years has helped to clarify the long-term efficacy, safety, and tolerability of VNS in patients with epilepsy.

Clinical trials. Approval of VNS therapy by the FDA for adjunctive treatment of refractory partial seizures followed a series of clinical trials. Beginning in 1988 with a pilot trial,[3] the studies progressed through two pivotal trials, both multicenter, double-blind, randomized, parallel, active-control studies of VNS therapy. The first pivotal trial, the E03 study, evaluated 114 patients with predominantly partial seizures[4-7] and the second, E05, included 199 patients with complex partial seizures.[8] The E04 study, a compassionate-use trial, included 124 patients with all types of intractable seizures.[9]

In the pivotal trials, baseline seizure frequencies were prospectively established during the 12 to 16 weeks before implantation. Changes in AEDs were permitted only to maintain appropriate concentrations or to respond to drug toxicity. Two weeks after patients were implanted with the VNS therapy system, they were randomly assigned to either high (30 Hz, 30 seconds on, 5 minutes off, 500 μsecond pulse width) or low (1 Hz, 30 seconds on, 90 to 180 minutes off, 130 μsecond pulse width) stimulation. The pivotal trials compared the percentage change in seizure frequency at baseline with that after treatment for both stimulation groups. In both pivotal trials, the mean percentage of seizure reduction was significantly greater in the high stimulation group, 24.5% versus 6.1% ($p = 0.01$) in the E03 study and 28% versus 15% ($p = 0.039$) in E05. Within-group comparisons of baseline and after-treatment seizure frequency were statistically significant ($p = 0.0001$) in both the high- and low-stimulation groups.[4-8] The table lists adverse events that occurred in the E05 study.

Long-term efficacy. Patients who completed the E03, E04, or E05 study entered a prospective 12-month study. Because treatment was unblinded (all patients received high stimulation) and AED adjustments were permitted, suggestions that efficacy improved with time should be viewed with caution. Compared with baseline seizure frequencies, median seizure reduction was 34% after 3 months and 45% after 12 months ($p = 0.0001$). Furthermore, at 12 months, 20% of the patients had seizure frequency reductions of 75% or more.[6,10-12]

AED reduction. Tatum et al. found that patient satisfaction improved and seizure control was not reduced when the numbers or dosages of AEDs were

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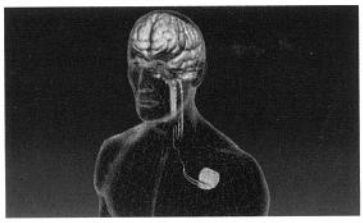

Figure 1. Schematic drawing of the general placement of the VNS therapy generator and bipolar stimulating lead. (Cover design; reproduced with permission).

reduced in 15 of the 21 patients participating in a 13-month prospective study.[13,14] Two of six of the patients in the same study were able to discontinue psychotropic drugs.

VNS therapy among special populations. VNS therapy has now been used in special populations characterized by patient age, epilepsy syndrome, and seizure type. Wheless and Maggio outline the effectiveness of VNS therapy among patients younger than 18 years in a separate article in this supplement.

Patients with generalized seizures. After 3 months of VNS therapy, a reduction of 46% in median seizure frequency was reported for 24 patients with pharmacoresistant generalized seizures and only generalized epileptiform activity or generalized EEG slowing. Seven of the patients had idiopathic epilepsy and 17 had symptomatic epilepsy. Seizure frequency reductions of 50% or more were noted in 11 patients. Interestingly, patients whose epilepsy began at older ages and with higher seizure rates at baseline had the most favorable responses to VNS therapy.

Table *Treatment-phase adverse events among patients treated with low or high VNS therapy in the E05 study**

Adverse event	Low stimulation (n = 103) (n (%))	High stimulation (n = 95) (n (%))
Accidental injury	13 (12.6)	12 (12.6)
Cough	44 (42.7)†	43 (45.3)†
Dyspepsia	13 (12.6)	17 (17.9)
Dyspnea	11 (10.7)	24 (25.3)‡
Fever	19 (18.4)	11 (11.6)
Headache	24 (23.3)	23 (24.2)
Infection	12 (11.7)	11 (11.6)
Nausea	21 (20.4)	14 (14.7)
Pain	31 (30.1)	27 (28.4)
Paresthesia	26 (25.2)	17 (17.9)
Pharyngitis	26 (25.2)†	33 (34.7)†
Voice alteration	31 (30.1)	63 (66.3)§
Vomiting	14 (13.6)	17 (17.9)

* Only adverse events that occurred in more than 10% of high-stimulation patients are listed.
† $p < 0.0001$, within-group, McNemar's test for matched pairs with dichotomous outcomes.
‡ $p = 0.007$, between-groups comparison, χ^2 test.
§ $p = 0.001$, between-groups comparison, χ^2 test.

Adults aged 50 years and older. The tolerability, safety, and effectiveness of VNS therapy among older adults was evaluated by Sirven et al.[16] among 45 patients aged 50 years and older. Reductions of 50% or more in seizure frequency were noted among 12 patients after 3 months of VNS therapy and among 21 of 31 patients after 12 months. Marked improvements were noted in quality of life, and side effects were described as transient and mild.

VNS therapy in co-morbid conditions. *Memory.* A study showing that post-training stimulation of the vagus nerve enhanced memory storage in rats[17] provided impetus for a study of word recognition memory among patients in the VNS clinical trials.[18] After reading paragraphs with highlighted words, patients received either VNS or sham stimulation. The investigators found that VNS, but not sham stimulation, significantly enhanced retention of verbal learning (word recognition), supporting their hypothesis that activation of the vagus nerve modulates memory formation similarly to arousal. The implications of these findings are unclear for epilepsy patients with memory dysfunction. Another memory study involving 11 patients showed a "fully reversible" worsening of figural recognition memory when VNS was delivered during the task.[19] Verbal recognition performance was unaffected, and decision times were accelerated.

Mood. Two studies have noted improved mood lasting as long as 6 months among epilepsy patients receiving VNS therapy.[20,21] Both studies indicated that mood improvement was independent of seizure reduction. In another study, mood and health-related quality of life were assessed with self-report questionnaires.[22] The 28 patients had received 6 months of VNS therapy, were receiving stable AEDs, and had low baseline depression scores. Tenseness, negative arousal, and dysphoria were noted as improved. Although depression scores did not improve, they were low at baseline.

Hypothalamic hamartomas. Among six patients with hypothalamic hamartomas who received VNS therapy, distinct improvements in behavior were noted in four. The change was immediate and was not associated with the degree of seizure reduction. All four of the children with improved behavior were autistic and three of them were mentally retarded. When stimulation was stopped for 2 weeks in one patient who underwent surgery, the negative behavior returned, but it resolved when stimulation resumed.[23]

Cognitive function. Cognitive testing of 160 patients in the E05 study with the Wonderlic Personnel Test, Digit Cancellation, Stroop Test, and Symbol Digit Modalities Test showed no significant differences between the high- and low-stimulation treatment groups during the baseline-to-treatment period.[24] Cognitive studies (attention, motor func-

tioning, short-term memory, learning and memory, and executive functions) of 36 patients before and a minimum of 6 months after VNS implantation found no evidence of worsened cognitive function.[25,26]

Excessive daytime somnolence. Malow et al.[27] performed polysomnography and multiple sleep latency testing on 15 patients who were receiving VNS therapy. They found daytime sleepiness to be reduced and REM sleep enhanced. Such changes occurred irrespective of reductions in seizure frequency.

Developmentally disabled and mentally retarded patients. A retrospective record review by Andriola and Vitale[28] stated that 11 of 16 developmentally disabled patients experienced a 50% or greater reduction in seizure frequency after 6 months of VNS therapy. In a comparison of patients living in residential treatment facilities (RTFs) receiving VNS therapy with others not living in RTFs, Gates et al.[29] found that median reductions in seizures were significantly different between groups after 3 months but not after 12 months. They noted that the advantages of VNS therapy for the RTF population included its lack of interaction with medications and automatic delivery.

Quality of life. An open study of quality of life (QOL) changes of 136 adults measured the difference in questionnaire responses at baseline and after 3 months of VNS therapy. Patients who experienced a 50% or greater reduction in seizures had statistically significant improvements in energy, memory, social aspects, mental effects, and fear of seizures. Downheartedness and overall QOL improved in patients with lesser seizure reductions. Although placebo effect cannot be ruled out in this study, VNS may exert a positive effect on QOL that is independent of seizure reduction.[30] Eight patients were asked to rate their QOL regarding limitations at home, at work, and socially both at baseline and after 12 months of VNS therapy. A comparison of the responses did not show a reduction in limitations at 12 months.[31]

Safety and tolerability. An article in this supplement by Heck et al. reviews VNS stimulation parameters and explains some safety features of the VNS therapy system.

Several features of the VNS therapy system safeguard against excessive stimulation that might damage tissue. The stimulation parameters in typical clinical use have not been shown to damage the vagus nerve.[32-34] Patients or their caregivers can turn off the stimulation at any time by keeping the VNS magnet over the pulse generator. This measure can be taken when stimulation becomes uncomfortable or when the patient wants to avoid vocal variation while speaking, singing, or playing wind or brass instruments for an extended period.

Microwave transmission, cellular telephones, and airport systems do not affect the VNS therapy generator or electrode leads. However, the manufacturer does specify some restrictions in the use of MRI. In theory, a body MRI could heat the electrode leads and thereby damage local tissue. When used according to the manufacturer's guidelines, a brain MRI conducted with a send-and-receive head coil is safe.

Twelve of 40 epilepsy centers responded to a survey on MRI testing of patients implanted with the VNS therapy system. Of the 27 scans performed in 25 patients, 26 used a head coil and one used a body coil. In accordance with the manufacturer's recommendations, 24 scans were performed with the stimulator off but three were done with the stimulator on. A mild voice change was noted in one patient, and a child, aged 11 years, experienced severe claustrophobia and complained of chest pain. No other adverse events were reported. Benbadis et al.[35] conclude that the results of their survey support the safety of performing routine brain MRIs with a send-and-receive head coil in patients with the VNS therapy system. However, the authors also point out that functional MRI (fMRI), which may use higher magnetic fields, may not be as safe as conventional MRI. However, there is at least one report of safe fMRI use with VNS therapy.[36]

In a review of VNS therapy side effects and long-term safety, Ben-Menachem[37] outlined adverse events reported over the 12 years that VNS has been used in humans. Characterizing the side effects as mild to moderate and resolving with time, the author notes that VNS therapy does not produce the CNS side effects that sometimes limit the use of AEDs. Complications associated with implantation have included infection at the incision, which required antibiotics and rarely removal of the device or electrodes, and transient paralysis of the left vocal cord.

Among both children and adults, the most commonly reported side effects are voice alteration, hoarseness, throat or neck pain, headache, cough, and dyspnea. These side effects are often most evident during stimulation, can sometimes be lessened by adjusting device stimulation parameters, and tend to diminish with time.[37]

Adverse events among pediatric patients. About 1 year after VNS therapy was approved by the FDA, Murphy et al.[38] reported on the adverse events in 24 pediatric patients implanted with the VNS therapy system. Fifteen adverse events occurred in 11 patients. One patient had four adverse events and two patients had two adverse events each. Lead fractures accounted for five adverse events, wound erythema for two, removal requested by two, and one each for abscess, generator malfunction, gastrostomy, prégnancy, recurrent psychosis, and diminution of speech volume during stimulation. Remedying these adverse events entailed 11 surgical procedures and the inherent risks of general anesthesia and a venous line. Six of these procedures resulted from problems with either the leads or generator failure. Since publication of this report, the manufacturer has introduced improved leads and generator, and

reports of VNS therapy system failures have greatly diminished.

Histologic studies of vagus nerves of adult patients who have received VNS therapy showed similar cellular changes (attributable to post-mortem preservation artifacts) to both pulsed and unpulsed nerves.[34] However, a recent autopsy report of a patient aged 5 years who had received VNS therapy noted changes in the pulsed vagus nerve compared with that of a patient aged 10 years who had not received VNS therapy.[39]

Safety and isolated adverse events. The mortality and rates of sudden death in epilepsy (SUDEP) of patients receiving VNS therapy are comparable with those of other groups of patients with medically refractory seizures. A comparison of 3,176 person-years of VNS therapy (1,819 patients) with cohorts of young adults with refractory seizures who did not receive VNS yielded similar mortality rates and standardized mortality ratios. The SUDEP rate during the first 2 years patients received VNS therapy was 5.5 per 1,000 person-years. Interestingly, the rate decreased to 1.7 during the follow-up period after the initial 2 years.[40]

Several isolated occurrences of adverse events related to VNS therapy have appeared in the literature. One patient, aged 20 years, had spasms of the sternocleidomastoid muscle when VNS intensity was increased to 2 mA. The authors attributed the spasms either to the stimulation occurring near the accessory nerve or to an anastomosis between the vagal and accessory nerves.[41] A patient with preexisting hemorrhoids developed chronic diarrhea when stimulator intensity was increased after implantation. The authors hypothesized that the diarrhea was an idiosyncratic response.[42] Horner syndrome developed in one patient after implantation.[43] Other anecdotal reports include posture-dependent stimulation of the phrenic nerve,[44] obstructive sleep apnea present before implantation and worse afterward,[45] dysphoric disorders present before implantation and intensified when VNS reduced seizures,[46] and transient (up to 20 seconds) asystole observed in nine patients (0.1% of all implantations) during the lead test conducted during implantation to assess device integrity, as mentioned above.[47-49] The device was removed immediately from four of the patients, and the remaining five received VNS therapy. No sequelae were reported for any of the nine patients.

In addition, some patients experience vocal changes with VNS therapy that Charous et al.[50] reported were associated with the intensity of stimulation: the lower the stimulation, the less the effect. They further noted a potential for airway compromise among patients with undiagnosed right-sided vocal cord paralysis or partially obstructing laryngeal lesions. Zumsteg et al.[51] reported on three VNS therapy patients who underwent fiberoptic laryngoscopy. The authors suggest that vocal cord adduction may be the physiologic correlate of the voice alteration, throat pain, and perhaps even dyspnea and coughing sometimes reported with VNS therapy. Severe mental and motor retardation, coupled with a need for assistance with feeding, may increase the risk for aspiration among children implanted with the VNS therapy system if VNS occurs while they are being fed.[52] Swallowing difficulties, as evidenced by laryngeal penetration of barium, were observed in three of eight children and attributed to VNS in a fourth, but no aspiration occurred among these eight children.[53]

During August of 2001, Cyberonics, Inc. issued a Safety Alert advising against the use of short-wave, microwave, or therapeutic ultrasound diathermy for persons implanted with the VNS therapy system. Although no injuries have been associated with diathermy treatment among VNS patients, the potential exists for diathermy treatment to heat the generator or leads and damage tissue or cause discomfort. No precautions regarding diagnostic ultrasound were listed.

Clinical application of VNS therapy. Implementing a successful program of VNS therapy entails a collaborative approach among health-care professionals to provide patient education, surgical implantation, and office visits for device programming.[54] The exact role of VNS in the treatment of seizure disorders is still evolving. Clinicians who follow VNS therapy patients are faced with three practical problems: (a) the lack of a well-defined profile for identifying candidates who are most likely to respond to VNS therapy; (b) the lack of a measurable physiologic response with which to gauge the individual patient's device settings and response; and (c) the initially high cost of the VNS therapy system and implantation. Such limitations provide the basis for discussions of the appropriate role of VNS therapy for epilepsy.[55] Nevertheless, VNS therapy should be one of the treatments considered for patients with partial-onset seizures that have not been satisfactorily controlled after two to four trials of appropriate AEDs as monotherapy or polytherapy.

Some clinicians increase stimulation protocols if patients have not achieved satisfactory seizure reduction within 3 to 6 months of implantation (figure 2). Efficacy has been improved in some patients by reducing stimulation "off" time to 1.8 minutes from the 5 minutes used for "high" stimulation in the E03 and E05 studies.[56] In addition, open studies have shown improvements in efficacy, tolerability, and QOL over time. Therefore, clinicians should not prematurely conclude that VNS therapy has not been effective because the onset of efficacy may have been delayed. It is appropriate to continue VNS therapy for at least 1 year, and up to 2 years, before discontinuing it owing to inefficacy. Although data on the use of VNS therapy for generalized seizures are encouraging, they are derived from open, uncontrolled studies, and therefore deserve further investigation

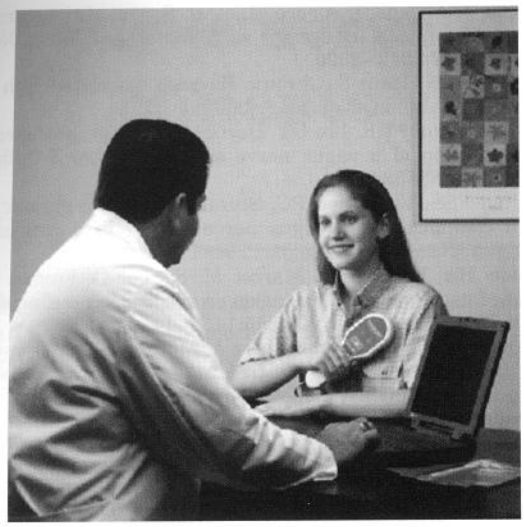

Figure 2. Use of programming wand to adjust generator stimulator parameters. Photo courtesy of Cyberonics, Inc.

with controlled studies. With regard to cost, the savings in direct medical expenses for some patients during the 2 years after implantation can offset the initially high cost of VNS therapy.[56,57]

Summary. More than 16,000 patients have been implanted with the VNS therapy system. The 5 years since FDA approval have shown that VNS therapy is effective, safe, well-tolerated, and an appropriate treatment to consider for patients with medically refractory partial-onset seizures whose seizures have failed to satisfactorily improve with at least two to four AED trials.

The decision to recommend VNS therapy entails two considerations. First, the patient's appropriateness as a candidate for surgical resection and response to previous AED therapy should be taken into account. Second, the efficacy of VNS therapy, its potential positive effects on QOL, and the possibility for eventual AED reductions must be weighed against the surgical aspects of the implantation procedure, the potential adverse events, and the possibility that seizure severity or frequency will not improve. Therefore, patients with partial-onset seizures should be considered for VNS therapy if their seizures have not responded to two to four trials of appropriate AEDs and if they are either not good candidates for surgical resection or are good candidates but refuse to undergo intracranial surgery.

Additional studies should investigate further the (a) efficacy of VNS therapy in reducing generalized seizures, (b) maximization of the effectiveness of VNS therapy, (c) potential synergistic combinations of VNS therapy with AEDs and other medications, (d) identification of suitable candidates for VNS therapy, and (e) comparison of VNS therapy with other adjunctive AED therapies, particularly early in the course of epilepsy.

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Vagus nerve stimulation therapy in patients younger than 18 years

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Article abstract—Nonpharmacologic treatment options are effective in reducing seizures and improving quality of life without the negative side effects associated with antiepileptic drug (AED) therapy among pediatric epilepsy patients. One such treatment, vagus nerve stimulation (VNS) therapy, appears to be particularly effective among pediatric patients with refractory seizures. Seizure severity and frequency, as well as quality of life, are improved with VNS therapy.

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The goal of epilepsy treatment is to achieve seizure freedom with minimal side effects. For most epilepsy patients this goal is achieved with the use of a single antiepileptic drug (AED).[1] If monotherapy trials are ineffective in controlling seizures, a combination of two or more AEDs is traditionally used. However, the prognosis for seizure control by using additional AED therapies after failure of initial drug treatment is less than favorable.[2] Moreover, in children and adolescents the possible effect of multiple drug therapies on development is a special concern. The emergence of new treatment options over the past decade, including vagus nerve stimulation (VNS) therapy, the resurgence of interest in the ketogenic diet, and the growing experience with surgical interventions provides clinicians more opportunities to tailor treatments to individual patients and avoid the adverse effects of pharmacotherapy.

This article provides a review of VNS therapy in the pediatric population (patients younger than 18 years receiving treatment with VNS). A literature search of VNS therapy in children and the current VNS registry data provided by Cyberonics, Inc. (Houston, TX) were used as the basis of this review. The literature search was limited to VNS therapy experience in the United States.

Selection of epilepsy treatment for pediatric patients. Although new diagnostic techniques help to determine seizure etiology, seizure type, and epilepsy syndrome, the increased number of therapeutic options may make the selection of the appropriate treatment for each individual more complicated than previously. The current paradigm for initial treatment is to treat with monotherapy AED trials. If seizures are not controlled after two monotherapy trials and a single combination trial, then other treatments should be explored. Children with pharmacoresistant epilepsy should be evaluated for other treatments and a logical, tailored treatment strategy should be developed based on the likelihood of achieving control balanced against the potential risks for each therapy. These therapies can then be sequentially pursued to determine the optimal treatment for each child. Many experts now agree that nonpharmacologic options, including surgery, should be pursued earlier in the treatment course of intractable epilepsy.[1-3] Concerns regarding the adverse physiological effects of AEDs in the pediatric population make nonpharmacologic treatment options more attractive to clinicians who care for children.

Concerns about potential adverse effects of AEDs may result in a delay in initiating drug therapy in children with newly diagnosed epilepsy, particularly in those with certain etiologies.[4] These concerns have led to a resurgence of interest in the ketogenic diet. The ketogenic diet, first developed in the 1920s, was used less frequently as a treatment option after the development of AEDs, but is once again viewed as an option after failure of drug therapy in children with refractory epilepsy. The diet is more effective in children younger than 12 years compared with adolescents and adults. However, the program requires a level of commitment by both patients and families to comply with the strict dietary guidelines, which limits the application of this treatment to a relatively small proportion of epilepsy patients. Therefore, the ketogenic diet is often used only in children (a) with intractable seizures, (b) with intolerable side effects to AED therapy, or (c) with specific biochemical disorders as a cause of their epilepsy.[5]

If medical therapy is ineffective in controlling seizures, patients should be evaluated for surgical options. VNS therapy should be considered for patients who do not qualify for or who have not responded to a previous epilepsy surgery. Additional criteria for VNS therapy candidate selection are lacking owing to the broad spectrum of efficacy without regard to

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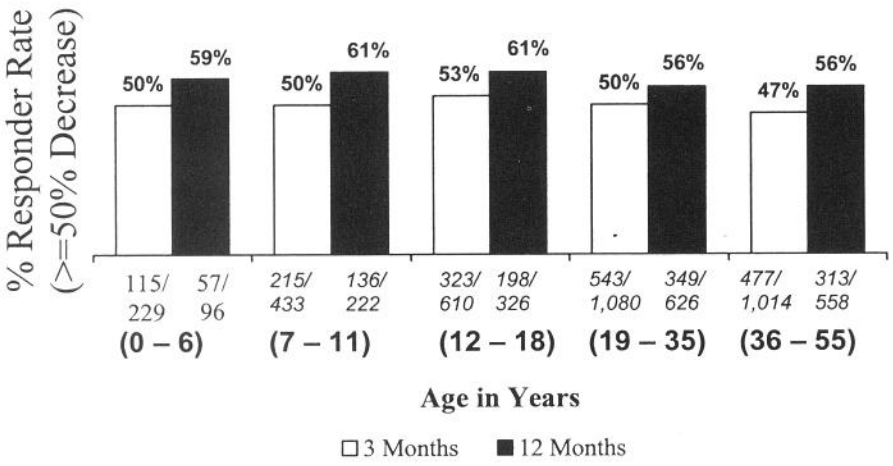

Figure 1. VNS therapy effectiveness by age group (data as of January, 2002 on file at Cyberonics).

seizure type or etiology. Early clinical trials did not find a predictive response to VNS therapy based on age, gender, seizure frequency, or the frequency of interictal spikes on EEG.[5]

VNS in the pediatric population. Although VNS was approved in the United States in 1997 for treatment of medically refractory, partial-onset seizures in epilepsy patients aged 12 years and older, the treatment appears to be equally effective in reducing seizures in children younger than 12 years (figure 1). As of January 2002, more than a quarter of the approximately 14,500 patients implanted with the pulse generator have been younger than 18 years, with half of them being younger than 12 years (figure 2). Of those pediatric VNS patients reviewed in the VNS patient outcome registry, the most common co-morbidity is mental retardation/developmental delay (MRDD), which affects 70.5% (figure 3). Children with developmental disabilities are more likely than developmentally normal children to have medically refractory epilepsy,[6,7] are at increased risk for prolonged seizures,[8-10] and are at increased risk for recurrent episodes of prolonged seizures.[11,12] Contrasted to the generally poor response of traditional AEDs in treating MRDD patients with epilepsy,[13] 61% of the pediatric VNS population had at least a 50% reduction in seizure frequency at 12 months. In addition, when this population was analyzed by the following age groups—0–6, 7–11, and 12–18 years, inclusive—more than half in each age group achieved at least a 50% reduction in seizures at 12 months. These findings are comparable with the 56% of patients aged 19 to 35 years reporting at least a 50% seizure reduction at the same time point (see figure 1).

These results indicate that age does not appear to be a factor in determining VNS treatment success. Pediatric patients may in fact have a better response than patients older than 18 years, as indicated by the slightly higher responder rates in patients younger versus patients older than 18 years (see figure 1). Early observations of VNS therapy in patients whose age range was 4 to 16 years also were suggestive of better responder rates in pediatric patients.[14]

In addition to seizure reductions, pediatric patients also show improvements in quality-of-life measures, including mood, alertness, verbal skills, memory, and school/professional achievements.[15-17] Such improvements in quality of life are not solely due to improved seizure control.[15,18,19] Recent studies evaluating VNS therapy patients less than 18 years of age report similar results of seizure control and improved quality of life.

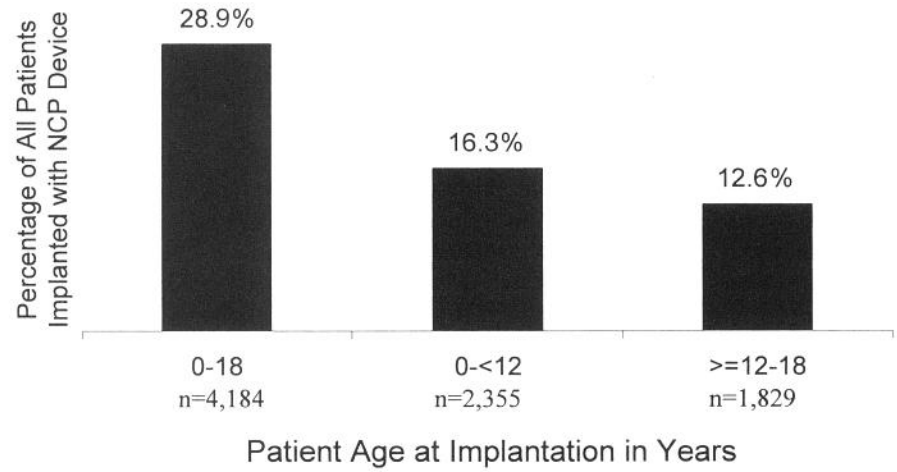

Figure 2. Percentage of all patients implanted with the VNS pulse generator younger than 18 years (data as of January, 2002 on file at Cyberonics).

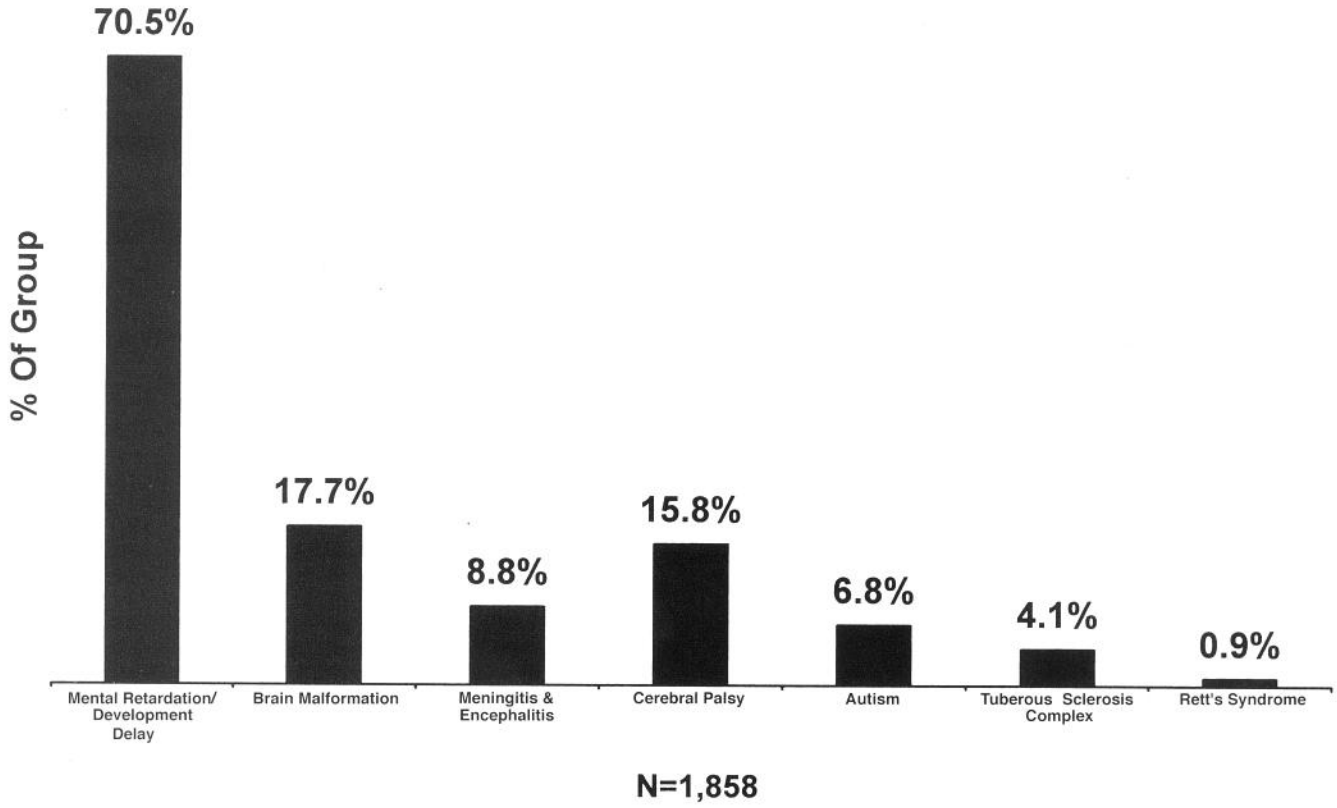

Figure 3. VNS therapy patient outcome registry: co-morbidities in pediatric patients receiving VNS therapy (data as of January 2002 on file at Cyberonics).

Recent studies in pediatric VNS patients. Similar to long-term results in patients older than 12 years,[20] improvements in seizure frequency and quality of life increase with time. In a recent single-center study of 38 children with medically refractory epilepsy, aged 11 months to 16 years, follow-up periods of at least 6 months were associated with statistically significant reductions in seizure frequency ($p = 0.05$) and higher quality-of-life scores ($p < 0.01$).[18] At a median follow-up of 12 months, 29% of the children experienced a greater than 90% reduction in seizure frequency and 86% were reported as having improved quality of life. Age and duration of epilepsy did not affect patient outcomes. Quality of life scores in this group were higher among patients with a shorter duration of epilepsy ($p = 0.08$), who had an onset of seizures after age 1 year ($p = 0.05$), and who had longer follow-up times ($p = 0.003$). Similar to previous quality-of-life findings in VNS therapy patients, improvement in quality of life did not correlate solely with seizure reduction.[15,18]

A retrospective study of the largest group of patients younger than 18 years ($n = 125$) found seizure frequency reductions greater than those in initial VNS therapy trials and comparable with reductions in adult populations.[21] The average age at implantation for this population was 12 years, with an average age at seizure onset of 3 years. At implantation, patients had previously tried an average of nine AEDs. Of the 95 patients with follow-up data at 3 months, 28% had more than a 75% decrease in seizure frequency, with two patients reporting no seizures. At 6 months the average seizure frequency reduction had improved for the 56 patients who had follow-up data available, and 30% experienced seizure frequency reductions of more than 75%. Both responders and nonresponders analyzed in this study reported improvements in quality of life.

These studies show that, among patients younger than 18 years, VNS therapy is an effective treatment that is free of major complications. This is in contrast to polytherapy regimens involving multiple AEDs that have the potential for complicated drug interactions and potential rare, life-threatening side effects. Improvements in seizure control and quality of life correlate with outcomes found in adult populations of VNS therapy patients. In addition, the more rapid response rates seen in younger patients may lead to a better quality of life by eliminating potentially harmful psychosocial issues associated with intractable seizures in childhood. Such results indicate a use for VNS therapy in patients with medically refractory epilepsy for whom surgery is either not an option or in whom surgery has failed, regardless of age (figure 4). Unlike other epilepsy treatments, patient improvement does not appear to be dependent on seizure type or cause.[18,22]

Patients with Lennox-Gastaut syndrome. VNS therapy appears to be particularly effective in treating drop attacks in patients with Lennox–Gastaut syndrome (LGS).[16,19,21,23] A multicenter retrospective

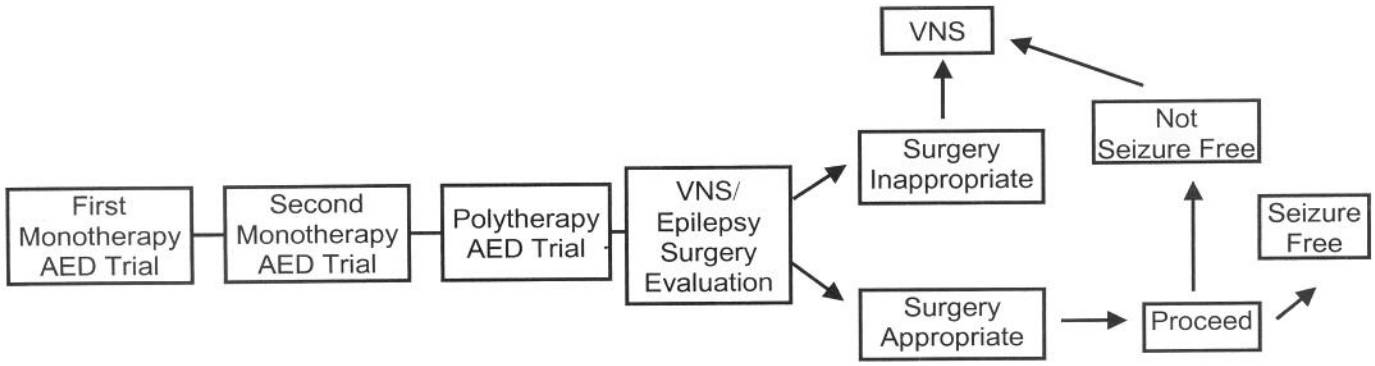

Figure 4. Treatment sequence for VNS therapy.

analysis of 43 pediatric patients with LGS characterized as having drop, atypical absence, and complex partial seizures revealed that more than one-third of the patients had greater than 75% reduction in seizure frequency when treated with VNS.[21] A separate retrospective study of 46 children with LGS showed improvements in all seizure types, including drop attacks.[16] These patients had a median age at implantation of 13 years (range 5 to 27 years). After 3 and 6 months of therapy in this group, improvements in quality of life were noted. This was particularly seen as enhanced alertness in more than half of the patients who had follow-up data available at 3 months (n = 43) and 6 months (n = 24). Improved quality of life was not necessarily associated with seizure control and should be investigated further in this group of patients.[16,19]

Patients with tuberous sclerosis complex. A review of medical records from several pediatric epilepsy centers found 10 patients with tuberous sclerosis complex treated with VNS for at least 6 months.[17] These patients, ranging in age at implantation from 7 to 20 years (mean age 13 years), had medically refractory seizures, averaging a mean of seven seizures a day and having been exposed to at least four AEDs before implantation. All 10 patients were mentally retarded. Nine of 10 patients experienced at least a 50% reduction in seizure frequency with VNS therapy, with 5 of the 10 patients having reductions of more than 90%. VNS therapy was well-tolerated in this population, with no major complications reported.

Patients with previous epilepsy surgery. A recent study indicates that pediatric patients undergoing epilepsy surgeries before implantation with the pulse generator respond differently to VNS therapy, depending on the type of surgery undergone.[21] Of the 33 patients who had previously undergone epilepsy surgery, 13 had a lobectomy, 18 had a callosotomy, and 2 had both a lobectomy and a callosotomy. With a median reduction in seizure frequency of 32% at 3 months, those patients with a previous lobectomy did not respond as well as those with a previous callosotomy, who had a median reduction of 79% at the same time point.

Side effects of VNS in the pediatric population. Common adverse events reported by VNS therapy patients, including voice alterations and cough during stimulation, also occur in the pediatric population. In the pediatric patients analyzed by Helmers et al.,[21] 57.9% experienced voice alteration and 37.9% experienced coughing. In children younger than 12 years, less common adverse effects occurring in approximately 1% of the population included an increase in drooling and ear pain.[21] A few patients reported an increase in hyperactivity, which is a side effect unique to this age group. Another patient experienced right-sided weakness and incoordination. Three patients reported broken leads. The majority of these side effects are rare, usually resolve over time and, if needed, can be immediately alleviated with changes in stimulation parameters to a pulse width of 250 μseconds and a frequency of 20 Hz.[21,24] Side effects of VNS therapy rarely require a cessation of treatment or explantation of the device in this population.

Conclusions. VNS treatment is often associated with improvements in patient quality of life and is one of the most well-tolerated, ongoing therapies now available for the treatment of epilepsy. Discontinuation rates of VNS therapy are lower than those found with all other available therapies. Other advantages of VNS therapy include minimal adverse events that typically resolve with time and no compliance issues. In addition, unlike other epilepsy treatments, VNS therapy appears to be successful regardless of seizure type or seizure cause, with improvements in seizure control increasing over time. Although the exact place of VNS therapy in relation to other available treatment options is still evolving, increasing recognition of the effectiveness of VNS therapy is likely to maximize its role in the treatment of epilepsy in both the pediatric and adult populations.

VNS therapy is not approved by the FDA for use in patients younger than 12 years. However, the nonpharmacologic aspects of this therapy make it particularly attractive for use in this population owing to the unique side effects and cognitive impairments associated with AED treatments, particularly

in MRDD patients. Experience with adjunctive VNS therapy in pediatric patients younger than 18 years who have intractable epilepsy has shown successful results comparable to those seen in adult VNS therapy patients.

At present, more than 4,000 patients aged 18 years or younger are being treated with VNS therapy. The efficacy of VNS therapy combined with the perhaps 10% of children diagnosed with epilepsy who may have intractable seizures[7] indicates that VNS therapy is underused in this population. A clinical trial in children that compares VNS therapy with medical management after failure of two AEDs is needed to provide further support for the use of VNS therapy earlier in the treatment course of children with intractable seizures.

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Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy

J. Ben Renfroe, MD; James W. Wheless, MD

Article abstract—Recent studies suggest that epilepsy that is unresponsive to medical therapy is likely to be refractory from the onset. Identifying such patients early and treating them with nonpharmacologic therapies may improve their outcome. We hypothesized that patients who had adjunctive therapy with vagus nerve stimulation (VNS) earlier in the course of their epilepsy would have a better response compared with patients who had VNS therapy instituted later in the course. Patients in the VNS patient outcome registry who were more than 5 years post onset of their seizure disorder at implantation and had seizure frequency data available at both baseline and 3 months comprised the control group (n = 2785). These data were obtained retrospectively. Patients who were implanted between August 15, 2000 and July 31, 2001 who had epilepsy for 5 years or less at implantation or who had tried four or fewer standard antiepileptic drugs (AEDs) before implantation, and who were evaluated at baseline and at 3-month intervals for seizure frequency and quality of life, comprised the early adjunctive registry (EAR group; n = 120). This group was identified prospectively by participating physicians at multiple centers. The data describe patient demographics, medical history, seizure frequency, and physician-graded quality of life measures. The two populations were demographically similar except for statistically significant differences in age, duration of epilepsy, institutionalized patients, and seizure type (partial and generalized). Although the median reduction in seizure frequency for all patients at 3 months was similar between groups (48.2% control versus 50.0% EAR), 15.0% of the patients in the EAR group reported no seizures at 3 months compared with 4.4% of those in the control group ($p < 0.001$). In addition, significantly more patients in the EAR group (20% versus 8%; $p < 0.001$) reported no seizures with alteration or loss of consciousness, and 32% of EAR patients reported no complex partial seizures compared with 17% in the control group ($p = 0.002$). Improvements in all areas of quality of life were reported by both populations, but more patients in the EAR group were reported as "much better/better" for postictal state ($p = 0.030$) and seizure clustering ($p = 0.002$). Typically, 5% of patients report having no seizures after 3 months of VNS therapy. The proportion increased threefold, from 5% to 15%, for patients who received VNS therapy earlier in the treatment process. Patients reported even higher rates of no seizures when simple partial seizures were excluded from the analysis or when only complex partial seizures were considered. Although these results are preliminary, they offer promise of success in achieving seizure control among patients with refractory seizures who have been diagnosed with epilepsy for less than 5 years or who have tried four or fewer AEDs. We suggest future prospective studies evaluating VNS therapy versus best medical therapy after the first two to three AEDs have failed, which typically occurs within 2 years of seizure onset.

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Although most patients with epilepsy achieve seizure control with minimal side effects with one antiepileptic drug (AED), more than 30% of patients do not receive adequate control with drug therapy, including treatment regimens with combinations of two or more AEDs. A recent study showed that, of 525 adult epilepsy patients, only 14% of patients who did not respond to treatment with the first AED became seizure-free with monotherapy using a second or third drug, and only 3% became seizure-free while receiving a combination of two drugs.[1] Results such as these suggest that a lack of response to initial AED therapy may be an indication of refractory epilepsy.

Other recent studies indicate that a second possible predictive factor for refractory epilepsy is the number of pretreatment seizures patients experience. A strong correlation exists between the number of seizures before AED therapy and their eventual remission on treatment, suggesting that AED-resistant epilepsy may be refractory from the onset.[1,2] On the basis of this hypothesis, many specialists are recommending evaluation of patients for nonpharmacologic treatment options earlier in their treatment course, i.e., after two first-line AEDs fail to control seizures.[1,3-5] Such options include resective surgery, the ketogenic diet, and vagus nerve stimulation (VNS) therapy. Identifying patients with refractory epilepsy early during treatment and offering them potentially effective nonpharmacologic treatments may greatly benefit them by improving

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outcome and curtailing the potentially irreversible psychosocial consequences of continuing seizures.[1,3]

Patients treated with VNS therapy in a multicenter, double-blind, randomized study had an average duration of epilepsy of 23 years, high seizure frequencies, and failed treatment with approximately seven AEDs.[6] Those patients randomized to receive high stimulation ($n = 103$) experienced a mean seizure frequency reduction of 27.9% compared with baseline. Patients who received low stimulation ($n = 95$) experienced a mean reduction of 15.2%. This prospective analysis focuses on earlier treatment with VNS than has typically been the case, to determine whether earlier VNS treatment further improves efficacy, i.e., patients within 5 years after epilepsy onset or who have tried four or fewer AEDs.

Methods. Data used for the control group in this analysis were taken retrospectively from the Cyberonics, Inc. (Houston, TX) VNS patient outcome registry. The registry was established in 1998 to monitor several aspects of VNS therapy patient outcomes since the treatment device received approval by the FDA. A detailed description of the registry is provided in another article in this supplement.[7]

The constant cohort used for the control group consisted of those VNS registry patients who were more than 5 years postonset of their epilepsy diagnosis at implantation and had seizure frequency and quality-of-life data available at both baseline and 3 months ($n = 2785$). Data for the early adjunctive registry (EAR) group were collected prospectively from multiple centers by participating physicians who treated patients implanted with the pulse generator between August 15, 2000 and July 31, 2001. Patients had been diagnosed with epilepsy for 5 years or less or had tried four or fewer AEDs before implantation ($n = 120$). This analysis includes only those patients with seizure frequency and quality-of-life data collected at baseline and 3 months. Patient demographics, medical history, seizure frequency, and physician-graded quality of life were considered in the analysis of the two groups.

In line with the standard medical practice for treating patients with VNS therapy, investigators adjusted the stimulation parameters for each patient according to the clinical response. AEDs were not changed, if possible, for the first 3 months of VNS treatment.

Results. *Medical history and demographics.* Based on the Fisher's exact test, patients in the control group compared with patients in the EAR group were similar in terms of medical history except for a significantly higher percentage of those in the control group being evaluated for epilepsy surgery ($p < 0.001$), receiving a previous callosotomy for epilepsy ($p < 0.006$), receiving a previous lobectomy for epilepsy ($p < 0.011$), experiencing behavioral problems ($p < 0.015$), and who were mentally retarded ($p = 0.003$) compared with those patients in the EAR group (table 1). The demographic characteristics of the two groups are shown in table 2. Patients in the control group were older in terms of mean age ($p < 0.001$) and median age ($p < 0.001$), and had a significantly longer mean duration of epilepsy ($p < 0.001$) compared with the EAR group. The control group also was composed of more institutionalized patients ($p = 0.002$) and more patients experiencing partial seizures ($p = 0.006$). Significantly more patients in the EAR group experienced generalized seizures ($p = 0.008$).

Table 1 *Medical history**

	Control (%)	EAR (%)	p Value
Congenital brain malformation	12.2	16.2	NS
Meningitis/encephalitis	11.7	6.0	NS
Vascular brain malformation	2.6	1.8	NS
Evaluated for epilepsy surgery	58.3	22.8	<0.001
Intracranial surgery			
Previous callosotomy for epilepsy	5.7	0.0	0.006
Previous lobectomy for epilepsy	10.7	3.1	0.011
Other (for epilepsy)	7.1	4.8	NS
Other (any intracranial surgery)	7.5	7.3	NS
Brain tumor	4.1	3.5	NS
Head injury	16.6	9.7	NS
Febrile seizures	11.4	11.7	NS
Psychosocial/psychiatric disorders	25.3	17.0	NS
Depression	24.9	24.5	NS
Behavioral problems	27.0	16.4	0.015
Neurologic defect	37.6	33.9	NS
Mental retardation	54.1	39.1	0.003
Developmental delay	52.3	54.0	NS
Cerebral palsy	14.2	19.3	NS
Autism	6.0	2.8	NS
Rett's syndrome	0.7	0.0	NS
Tuberous sclerosis	4.0	5.4	NS
Major surgical procedures	17.5	21.1	NS
Chronic illness	14.8	17.9	NS
Other	30.0	27.8	NS

* Data may be unavailable for some patients for some patient history items.

Seizure frequency. Before implantation, the median number of seizures per day was 0.9 (range 0–1071.3) for the control group and 1.1 (range 0–108.2) for the EAR group (NS). The median reduction in seizure frequency for all patients at 3 months was similar between groups, with 48.2% in the control versus 50.0% in the EAR group. No significant differences were found in the median percent change in seizure frequency for all seizures combined or for any grouping of seizure type analyzed (table 3). However, 15% of the patients in the EAR group reported no seizures at 3 months compared with 4.4% of those in the control group ($p < 0.001$) (figure 1). In addition, 20% of patients in the EAR group reported experiencing no seizures with alteration or loss of consciousness (seizures other than simple partial) at 3 months compared with 8% in the control group ($p < 0.001$) (figure 2A). The percentage of patients experiencing any increase in seizure frequency for seizures excluding simple partial were similar (14.7% in the control versus 20.0% in the EAR group), as was the percentage of patients experiencing a greater than 25% increase in sei-

Table 2 *Patient demographics*

	Control	EAR	*p* Value
Number of patients	2,785	120	NS
Mean age (years)	28.9	18.7	<0.001
Median age in years (range)	28 (6–79)	12 (1–64)	<0.001
Mean age at onset of epilepsy (years)	7.2	11.2	NS
Median age at onset of epilepsy in years (range)	4 (0–65)	4 (0–56.5)	NS
Mean duration of epilepsy (years)	21.7	5.9	<0.001
Median seizures per day before implantation (range)	0.86 (0–1071.3)	1.09 (0–108.2)	NS
Gender			
Male (%)	52.9	55.8	NS
Female (%)	47.1	44.2	
Institutionalized (%)	12.7	3.5	0.002
Known etiology (%)	40.0	40.0	NS
Normal MRI (%)	49.7	57.6	NS
Seizure type (%)			
Partial	61.1	48.3	0.006
Generalized	23.2	34.2	0.008
Lennox-Gastaut	11.8	7.5	NS
Rolandic	0.04	0	NS
JME	0.4	0	NS
Other*	3.6	10.0	
Number of AEDs at implant (%)			
0	0.4	4.2	<0.001
1	12.2	15.8	
2	40.5	42.5	
3	36.1	25.8	
4	8.9	10.0	
5	1.9	1.7	

* Although a patient may experience seizures of more than one type, patients are counted only in the primary type noted. If no primary type is indicated, the patient is counted in the "other" category.

zure frequency (10.5% in the control versus 13.3% in the EAR group). Moreover, of EAR patients reporting complex partial seizures at baseline ($n = 71$), 32% reported having no complex partial seizures at 3 months compared with 17% in the control group ($p = 0.002$) (figure 2B). The percentage of patients experiencing complex partial seizures who showed any increase in seizure frequency was similar, with 15.0% in the control versus 16.9% in the EAR group. The percentage of patients experiencing more than a 25% increase in seizure frequency for complex partial seizures also was similar (11.1% in the control versus 11.3% in the EAR group).

Quality of life. Patients in both groups were reported as showing improvements in each quality-of-life measure. More patients in the EAR group than the control group were reported as improved for postictal state ($p = 0.030$) and seizure clustering ($p < 0.002$) (figure 3). The number of patients reported worse for both quality-of-life measures was similar between the two groups.

Discussion. Patients with epilepsy characterized by uncontrolled seizures face a variety of risks, including higher mortality rates, higher rates of accidents and injuries, a higher incidence of cognitive

Table 3 *Median percent change in seizure frequency:*†‡*

	Median % reduction in seizure frequency	
Seizure group	Control	EAR
All seizures	48.2	50.0
All seizures except simple partial seizures	52.9	62.0
Complex partial seizures	50.0	66.7
Generalized tonic–clonic seizures	63.6	85.0
Secondarily generalized tonic–clonic seizures	66.7	84.6
Absence	80.1	83.7
Drop attack	75.0	66.1
Complex partial seizures and secondarily generalized tonic–clonic seizures	52.3	75.5

* Upper and lower limits have been set at (−100%, 100%).
† No statistically significant differences were found in the median percent change in seizure frequency for any of the above groups.
‡ Patients experiencing multiple types of seizures are included in each group for which they experienced a seizure.

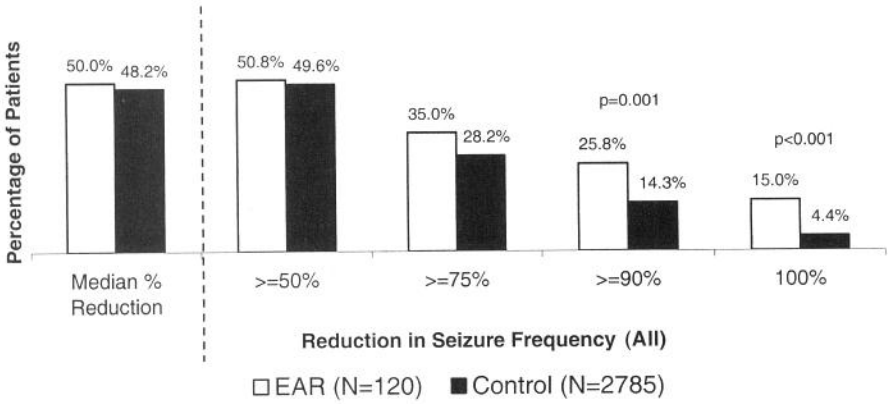

Figure 1. Reduction in seizure frequency at 3 months, all seizures.

and psychiatric impairments, poor self-esteem, higher levels of anxiety and depression, and social stigmatization or isolation.[8] Therefore, effective treatment to control seizures is fundamental to improving overall outcome. The ability to diagnose and treat medically refractory epilepsy early and with more aggressive therapies is hampered not only by the lack of predictive factors but also by the imprecise definition of refractory. Two factors that help to identify patients with refractory seizures earlier in the course of the disease include a high number of seizures and the fact that such patients are less likely to be helped by pharmacotherapy. Nonpharmacologic options such as surgery should not be considered a last resort in this population.[3]

Current guidelines published by the National Association of Epilepsy Centers suggest that, when a neurologist cannot control seizures within the first 12 months, other options should be considered.[9] We hypothesized that earlier nonpharmacologic treatment using VNS therapy in patients with medically refractory seizures would be more efficacious than later adjunctive use of VNS therapy. The results obtained by the analysis of early adjunctive treatment, considered to be VNS therapy system implantation within 5 years of onset or treatment with four or fewer AEDs before implantation, show promise in controlling refractory seizures among patients with epilepsy of a shorter duration.

The statistically significant differences between the groups in the medical histories and demographics were to be expected, given the larger population used for the control group. Even though the EAR group had a shorter duration of epilepsy (mean 6 years versus 22 years for the control group), it is important to note that these patients still represent a challenging treatment group, as reflected by the fact that the MRIs were abnormal in almost half of the patients (42.4%), seizure frequency averaged one per day, and 40% had a known etiology. Despite

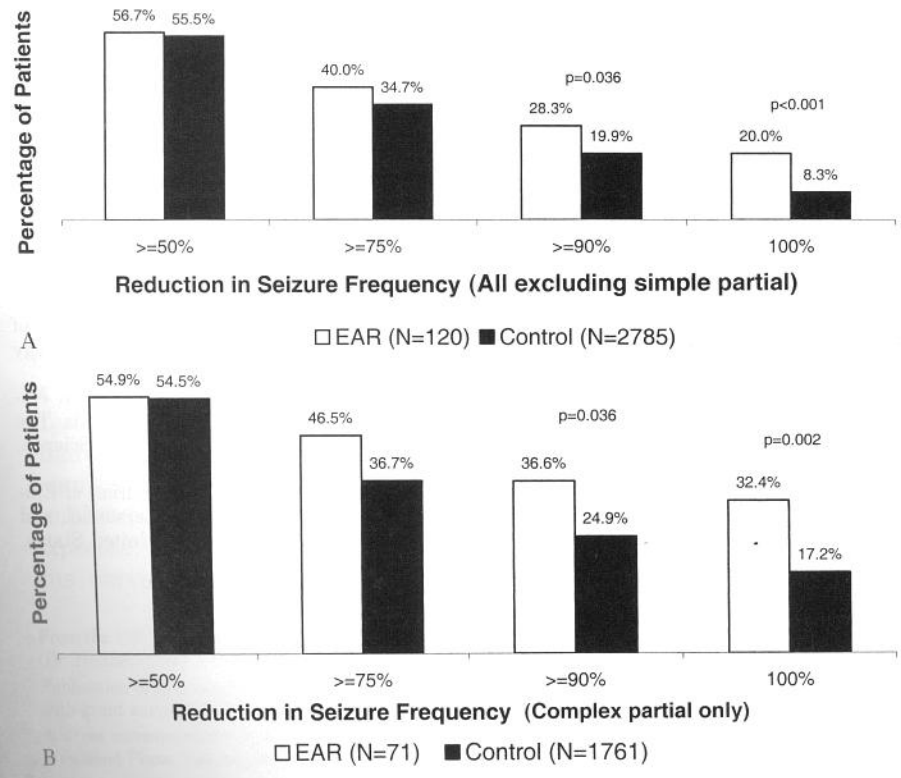

Figure 2(A). Percent change in seizure frequency at 3 months. Seizures with alteration or loss of consciousness (seizures excluding simple partial). (B) Percent change in seizure frequency at 3 months (complex partial seizures only).

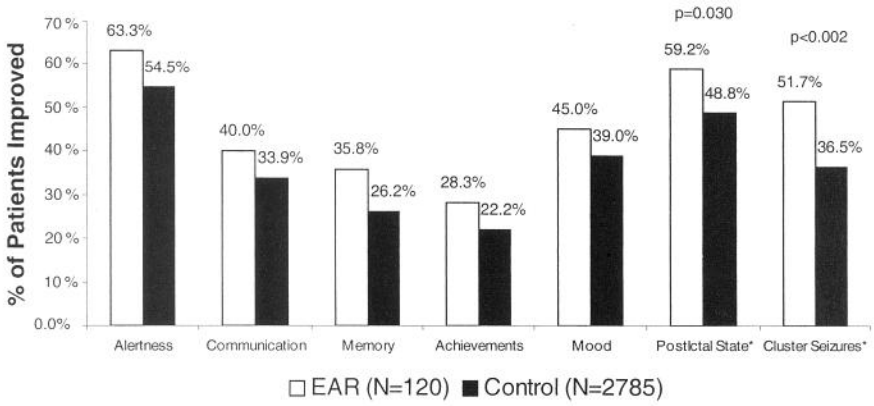

Figure 3. Quality of life at 3 months: percent of patients "better" or "much better."

these treatment challenges, 15% of all EAR patients reported no seizures of any type at 3 months, and 20% reported no seizures with alteration or loss of consciousness (seizures excluding simple partial). In addition, analysis of only complex partial seizures showed that 32% of EAR patients were free of such seizures after 3 months of VNS therapy. These reductions were all statistically significant compared with those of the control group. Moreover, although differences in the reductions in frequencies for other seizure types were not found to be statistically significant between the two groups, those differences may be clinically relevant.

Consistent with this improvement in seizure control were quality-of-life measures showing significant improvements in postictal state and seizure clustering. In addition, all other quality-of-life areas showed higher percentages of "much better/better" scores in the EAR group. These findings documenting improved seizure control and quality of life support the use of VNS therapy much earlier in the treatment of patients with pharmacoresistant epilepsy.

This study had several limitations. First, prospectively collected data were compared with data from an existing outcome registry. Data from a double-blind, randomized controlled trial would be considered much stronger. In addition, differences between the groups other than seizure duration might have influenced the results of this study. Efficacy was assessed only at 3 months. Patients should be followed for a longer period to determine whether the group differences persist.

Conclusions. We believe that pharmacoresistant epilepsies can be identified early in the disease course and that such patients should be evaluated for nonopharmacologic treatment options. These findings support this approach, offering promise of success in achieving seizure control and improving quality of life among patients with refractory seizures who have shorter durations of epilepsy than are now typically being treated with VNS therapy. A threefold improvement in 100% seizure frequency reduction was achieved among patients treated within 5 years after onset or after having tried four or fewer AEDs. At 3 months, one patient in five reported no seizures with a loss of consciousness, and one in three with complex partial seizures reported complete control of the complex partial seizures. The data indicate that earlier identification of appropriate candidates for VNS therapy (i.e., after two or three AED failures and duration of epilepsy less than 2 years) would enhance seizure control and subsequent quality of life. Future prospective studies using adjunctive VNS therapy versus medical therapy after failure of two or three AEDs are recommended and should be performed.

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Vagus nerve stimulation therapy, epilepsy, and device parameters

Scientific basis and recommendations for use

Christi Heck, MD; Sandra L. Helmers, MD; and Christopher M. DeGiorgio, MD

Article abstract—Our understanding of a precise dose-response relationship for vagus nerve stimulation (VNS) therapy in the treatment of seizures is still evolving. Because several parameters are involved in VNS therapy, the individual contribution of each is not well understood. This review discusses the efficacy of stimulation parameters used in the VNS clinical trials. The background, influence on safety and efficacy, and role in helping to achieve seizure control are discussed for each VNS device parameter: output current, pulse duration, frequency, and duty cycle. Finally, we provide an algorithm for the adjustment of VNS device settings (see Appendices).

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Vagus nerve stimulation (VNS) therapy is an effective adjunctive treatment for medically refractory epilepsy. In long-term clinical trials, the efficacy of VNS therapy improved over the first year of treatment to a median reduction of 45%.[1] The number of patients with robust (>75%) responses improved significantly by 1 year to 20% (figure 1).[1] The causes of this improvement are likely to be multifactorial. Because these studies are open-label, VNS-related factors could include increases in output current, shorter off times, increases in duty cycle (ON/ON+OFF), or a cumulative effect of VNS over time.[1,2] A central question remains: how do device settings affect safety and efficacy, side effects, or outcome?

Unlike most antiepileptic drugs (AEDs), a precise dose–response relationship for VNS therapy is still under investigation. Three pieces of evidence point to a dose–response relationship. First, two randomized trials have shown that "high" settings: 30 seconds ON, 5 minutes OFF at 30 Hz (0.25 to 3.5 mA) are significantly more effective than "low" settings: 30 seconds ON, 180 minutes OFF at 1 Hz (0.25 to 3.5 mA).[3,4] Second, when patients originally randomized to "low" settings were crossed over to "high" settings, a robust improvement in efficacy resulted[1] (figure 2). Third, when the duty cycle was increased above 22% or when OFF time was decreased to ≤1.1 minutes, a significant improvement in efficacy was observed (figure 3).[2] The amount of energy delivered to the vagus nerve (i.e., charge density) can be defined as amplitude * pulse width per unit time. As might be expected, the amount of energy delivered to the vagus nerve is dependent on output current and is increased with "high" and decreased with "low" stimulation. These observations have led us to believe that device settings clearly affect response. Because multiple variables are involved, the role of individual parameters remains poorly understood.

Because most patients do not become seizure-free on standard settings, intense interest has focused on alternative device settings for nonresponders.[2,5] This review evaluates the evidence, both preclinical and clinical, for a dose–response relationship of VNS therapy.

Effective device settings were first established in preclinical studies. The earlier preclinical studies used a cuff electrode that measured output current in volts (V), and the cuff used for later studies measured milliamperes (mA). Therefore, either measurement may appear in narratives of VNS preclinical studies. Zanchetti et al.[6] showed that interictal spikes in cats, produced by topical strychnine, were attenuated with VNS at 1 to 2 V, 50 Hz, and at pulse durations of 500 μseconds. Stoica and Tudor[7] also found that VNS, at 1 to 4 V, 30 Hz, and 300 μseconds, decreased the frequency of cortical spikes induced by strychnine. Zabara[8] reported that VNS at 5 to 15 mA, 80 to 150 Hz, and 500 to 600 μseconds, inhibited strychnine- and pentylenetetrazol-induced seizures in dogs. Woodbury and Woodbury[9-13] found that the optimal frequency for VNS in rat seizure models ranged from 10 to 30 Hz and the optimal pulse duration was 500 to 1,000 μseconds. Subsequently, Lockard et al.,[14] using settings of 5 mA, 50 to 250 Hz, and 500 μseconds, found that intermittent VNS with OFF times of 3 hours reduced seizures in monkeys. The discovery that intermittent VNS was antiepilep-

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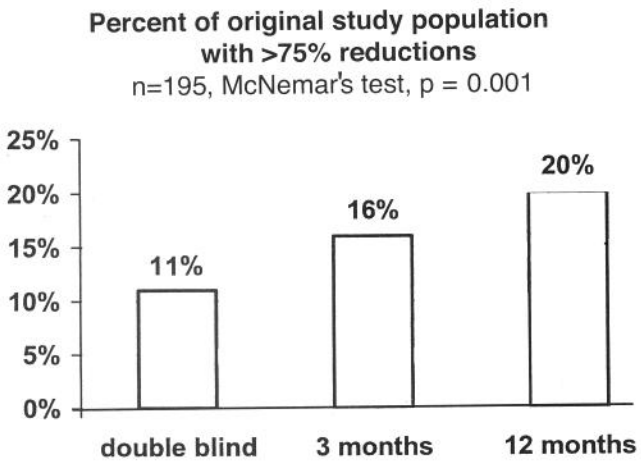

Figure 1. Percentage of the original study population (n = 195) who, at 3 and 12 months, have a greater than 75% reduction in seizures. Results at 3 and 12 months are compared with the "high" stimulation group at the end of double-blind study (McNemar's test; p = 0.001; 12 months versus double blind). From reference 2, with permission.

tic led to the development of intermittent VNS for human use. Subsequent experiments have found that intermittent VNS produces a cumulative anticonvulsant effect.[8,15] Agnew and McCreery[16] found that continuous high-frequency (≥50 Hz) stimulation could cause nerve injury and noted that the clinical protocols now in use for VNS are within a range that is unlikely to cause nerve injury.

Components of VNS. In humans, safe and effective VNS therapy is dependent primarily on output current, frequency, pulse duration, and ON and OFF time. This section discusses each of these components.

Output current. The vagus nerve is composed of three main fiber types: A, B, and C.[8,11,12,17,18] C-fibers are unmyelinated and therefore conduct more slowly. Most of the afferent fibers in the vagus nerve are C-fibers. C-fibers require markedly higher output currents (from 10- to 100-fold) to generate maximal action potentials. For example, at a pulse duration of 100 μseconds, A-fibers require an output current of

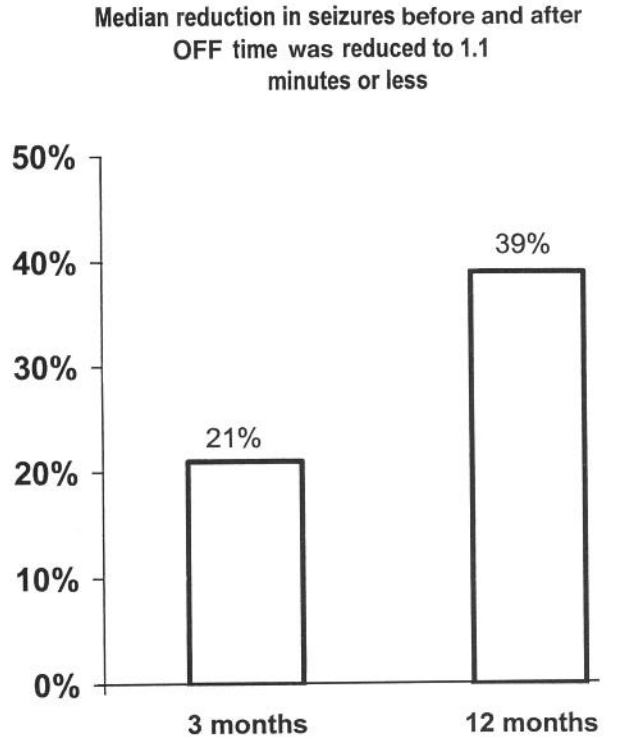

Figure 3. Median reduction in seizures at 3 months (before device change) and at 12 months (after device change). All comparisons are with the original preimplantation baseline. The change in seizure frequency from the 3-month visit to the 12-month visit was significant for the ≤ 1.1 minute OFF group (Wilcoxon signed rank test; p = 0.01).

less than 50 μA, whereas C-fibers require 600 μA. In the past, investigators postulated that C-fiber activation was critical for achieving the antiepileptic effect of VNS, and stimulation paradigms were therefore developed to provide maximum C-fiber activation.[9-13] However, current thought, as discussed in Henry's article elsewhere in this supplement,[19] points out that C-fibers are unlikely to be activated in humans. Output current is a double-edged sword, because excessively high output currents can affect safety in animals and tolerability in humans. In animals,

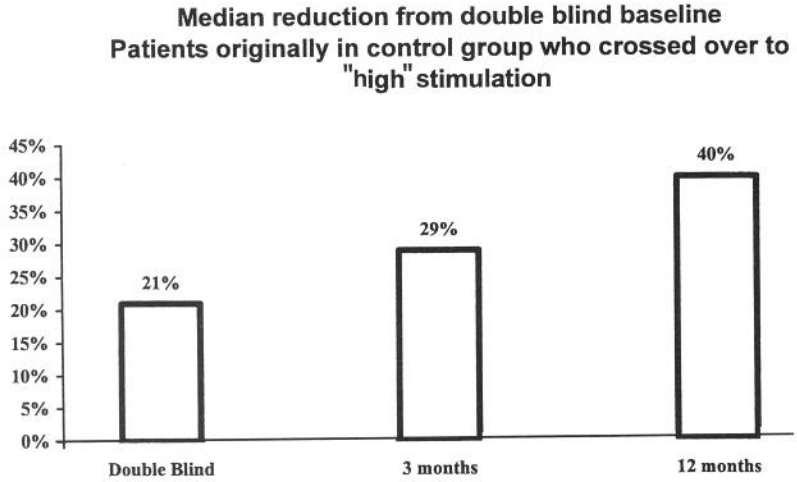

Figure 2. Reduction in seizures from baseline in patients crossed over from "low" settings, 30 seconds ON/180 minutes OFF at 1 Hz, to "high" settings, 30 seconds ON, 5 minutes OFF at 30 Hz. A progressive improvement in efficacy occurred after subjects were crossed over, providing evidence that changes in device settings do improve efficacy.[2]

heart rate is inversely related to output current intensity.[12] When output current is increased above the threshold for C-fiber activation, heart rate decreases.[12] Similarly, in humans, the output current must be set above the minimal level that provides effective stimulation and below levels that cause bradycardia, excessive throat tightness, and shortness of breath. Because later animal studies found that lower output currents, less than 5 mA, were effective, human stimulation was initiated at output currents of 1.0 mA and titrated upward to tolerance.[20] These output currents were very well-tolerated and patients tended to habituate, subsequently tolerating even higher output currents.[3] Fortunately, ECG and Holter monitoring in humans indicates that VNS is not associated with clinically relevant cardiac effects.[3,4] A safe stimulus range of 0.25 to 3.5 mA was used for all subsequent clinical trials, and the FDA approved stimulation at output currents of 3.5 mA or less.[3,4] It is not known whether higher output currents, if tolerated, would improve efficacy.

During VNS implantation, placement of the leads is tested with VNS parameters at an output current of 1 mA, pulse width of 500 μseconds, and frequency of 20 Hz. This test typically lasts less than 60 seconds and is the first delivery of VNS to the patient. Asystole and bradycardia have been reported in anesthetized patients during lead testing at 1 mA.[21] In these rare cases, a combination of anesthesia, manipulation of the vagus nerve, and stimulation may have contributed to the bradycardia. In some cases the electrode may have been placed near the cardiac nerve branches of the vagus nerve, resulting in excessive cardiac effects, or the polarity of the electrode may have been reversed (for a detailed review of possible causes and potential corrective actions, see Asconape et al.[21] and DeGiorgio et al.[22]).

Our understanding of the role of C-fibers in VNS is still evolving. Recent data indicate that C-fibers are not exclusively responsible for achieving efficacy and may not be necessary.[18] Capsaicin causes selective destruction of unmyelinated C-fibers. Krahl et al.[18] administered subcutaneous capsaicin to one group of rats and a sham solution to another group of rats. VNS was administered to both groups of rats, followed by an infusion of pentylene–tetrazol, a proconvulsant that is a major model for generalized seizures. A seizure severity score was calculated for each animal (0 to 6, ranging from no seizures (0) to hind limb extension (6). Despite the ablation of C-fibers before administration of pentylene–tetrazol, seizure severity was no different in the capsaicin-treated animals than in the control group. The authors theorized that the output currents commonly used for VNS are lower than the threshold required to achieve maximal C-fiber activation. Furthermore, they argued, if C-fibers were maximally stimulated, then noticeable or marked bradycardia or other autonomic changes would occur.[18] However, occurrence of bradycardia is extremely rare when FDA-approved VNS parameters are used.[3,4,21] This finding is important because high output currents or high pulse durations may not be necessary in all patients to achieve an anticonvulsant effect, given that C-fibers, which require higher intensity stimulation, are not central to the anticonvulsant effect of VNS.[18]

Table *Summary of changes in output current and ON/OFF time over 1 year of long-term follow-up*[2]

Device settings at 3 and 12 months of long-term treatment			
	End of double blind	12-month long-term study	Wilcoxon signed rank test
	(mean±SD)	(mean±SD)	*p* Value
Output current (mA)	1.1 ± 0.8	1.7 ± 0.8	<0.0001
OFF time (minutes)	5.0 ± 0.5	3.7 ± 2.3	<0.0001

Real-world experience suggests that as output current is increased, tolerability worsens. Side effects such as voice alteration, cough, throat tightness, and shortness of breath worsen with increasing output current. In the E05 trial, output current was gradually titrated upward to tolerance.[3] The mean output current at the completion of the 3-month treatment phase was 1.1 mA (high group, effective stimulation), with a fairly wide standard deviation of ±0.7 mA.[3] This range corresponds with most physicians' experience that average output currents of 0.50 to 1.5 mA are safe and effective and that higher output currents become progressively less well-tolerated. Fortunately, there is no evidence of clinically relevant bradycardia within the FDA-approved range of 0.25 to 3.5 mA but, in our experience, output currents above 2 mA are rarely necessary and can reduce patient tolerability.[3,4]

Does increasing output current improve efficacy? The answer to this question is poorly understood. No study has prospectively evaluated the effects of output current on seizure frequency. Although the long-term XE5 study was not designed to compare stimulation parameters, we may be able to infer a relationship from the data.[1]

First, efficacy had increased robustly after one year of VNS therapy. Both the median reduction in seizures and the 75% responder rates improved significantly[1] (figure 1). Second, output currents were significantly higher at 1 year of follow-up compared with the end of the 3-month double-blind treatment period.[1,2] This difference is summarized in the table. Third, output current tended to correlate with efficacy, but this correlation was just above the threshold for significance ($p = 0.056$, Spearman correlation).[1,2] Any potential correlation may have been compromised by the tendency of physicians to increase output current in nonresponders and to maintain output current in responders, thereby confounding the relationship between efficacy and increased output current.[1,2] Further research is

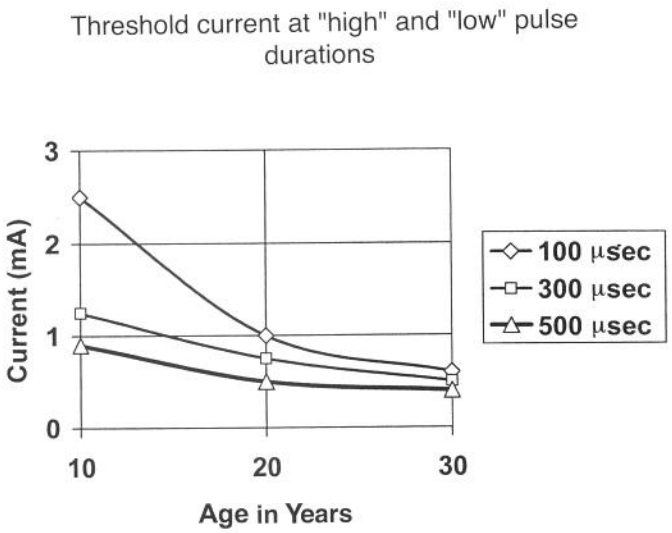

Figure 4. Output current necessary to generate vagus nerve compound action potentials. At "low" pulse durations, higher output current is required to generate a vagus nerve potential. This phenomenon is age-dependent.[8]

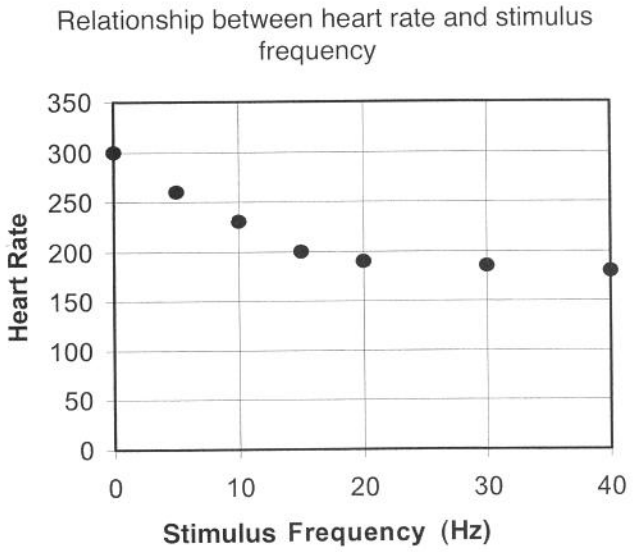

Figure 5. Relationship between heart rate and stimulus (Hz) frequency in rats. Adapted from reference 12, with permission.

needed to clarify the exact relationship between output current and efficacy.

Pulse duration. Once output current has been adequately adjusted, the physician can evaluate the feasibility of changing pulse duration.[12,23-25] Human intraoperative data indicate that pulse durations of less than 200 μseconds are likely to cause an increase in the threshold electrical current necessary to activate the vagus nerve. Higher-output currents are needed to generate vagus-nerve evoked potentials when the pulse duration is reduced to less than 200 μseconds.[8] This phenomenon is age-dependent. Younger subjects may require higher output currents. Figure 4 summarizes the relationship between pulse duration and output current.

Clinically, pulse duration affects the tolerability of VNS. Liporace et al.[25] and Labiner et al.[24] found that reductions in pulse duration from 500 μseconds to 250 μseconds increased tolerability. Animal studies have shown that efficacy is unaffected by a decreased pulse duration.[10] Patients who experience throat discomfort, cough, or shortness of breath at a specific output current may tolerate the output current when the pulse duration is decreased. Reducing the pulse duration from 500 μseconds to 250 μseconds improves tolerance to higher-output currents without loss of efficacy.[23] Few data are available describing the use of pulse durations of less than 250 μseconds in humans. Therefore, the use of such low pulse durations is not recommended unless the patient cannot tolerate the lowest output current with pulse durations of 250 μseconds.

Frequency. Preclinical studies found the optimal stimulus frequency to be between 20 and 30 Hz.[8-13] As early as 1966, Chase et al.[17] found that vagus-nerve evoked potentials were maximal at low stimulation frequencies of 20 Hz and were reduced at high frequencies of 200 Hz. Interestingly, EEG desynchronization (a marker of an anticonvulsant effect) was also enhanced at lower frequencies (<25 Hz).[17] Zabara[8] found that maximal anticonvulsant effect occurred at frequencies from 20 Hz to 30 Hz and that frequencies greater than 60 Hz tended to be less efficacious.

In preclinical studies of rats, Woodbury and Woodbury[12] found that heart rate was dependent on the frequency of VNS. When C-fibers were maximally stimulated, heart rate decreased with an increase in signal frequency. At 1 Hz, the heart rate in rodents was approximately 300/minute; at 20 Hz, the heart rate decreased to approximately 200/min. Heart rate continued to decrease as signal frequency increased, but the size of the reduction tapered (figure 5).[12] The reduced effect on heart rate at higher frequencies may occur because most of the efferent fibers from the vagus nerve to the heart are unmyelinated C-fibers,[8-13] which are slow conducting.[8-13,18] Therefore, low-frequency stimulation is more likely to maximally stimulate C-fibers.[8-13,18] C-fibers may become refractory to high frequencies and therefore are less affected by higher-frequency stimulation. This phenomenon explains the relative leveling off of changes in heart rate at higher stimulation intensities.[12] These findings have subsequently been extrapolated to human application.

Duty Cycles. The duty cycles (ON/OFF times) currently considered safe were first established for humans in the early 1990s.[20] In the initial phase I clinical trials, Uthman et al.[20] initiated VNS therapy at ON times of 60 seconds and OFF times of 60 minutes. OFF times were gradually reduced to every 5 minutes, the primary OFF time used for active-treatment groups in the pivotal E03 and E05 multicenter studies.[3,4] The VNS clinical trials showed that the duty cycle of 30 seconds ON and 5 minutes OFF

used in these trials was safe and effective, which led to the FDA approval of VNS therapy in 1997.[3,4]

At the conclusion of the pivotal E05 double-blind trial, patients were offered enrollment in the long-term efficacy and safety study (the XE5 study).[1] This study provided the first opportunity to analyze the effects of changing device settings.[1,2] After a 3-month delay to allow the "low"-stimulation group (active control group) to adapt to "high" (treatment) settings, physicians were free to adjust ON times, OFF times, and other device parameters within the range of settings later approved by the FDA.[2] Outcomes of patients whose duty cycles remained at 30 seconds ON and 5 minutes OFF were compared with those whose OFF times were changed to 3 minutes, 1.8 minutes, and ≤1.1 minutes.[2] The group that underwent a reduction in OFF time to ≤1.1 minutes (increase in duty cycle to >22%) showed a significant reduction in seizures: 21% reduction from baseline at the 3-month XE5 visit to 39% reduction from baseline at the 12-month XE5 visit (Wilcoxon signed rank test; $p = 0.01$).[2] Seizures were reduced by 50% or more in 19% of 26 subjects at 3 months and in 35% at 12 months (McNemar's test; $p < 0.05$).[2] Therefore, in patients for whom standard duty cycles are ineffective, a decrease in OFF time to 1.1 minutes or less or increases in duty cycle of greater than 22% may improve response.[2] A recent report found no difference in response when the initial standard duty cycle was compared with the initial rapid cycle.[26] However, the authors did not evaluate the effect of changing the duty cycle in nonresponders.

The New Parameters Trial. To examine the effects of alternative device parameters within the first 3 months of treatment, newly implanted patients were offered enrollment in an ongoing randomized trial of three unique duty cycles. Data are complete for 61 patients.[27] AEDs were unchanged for the initial 4-week baseline and 3-month treatment period. After a 1-month baseline period, patients were implanted with a VNS device and randomly assigned to one of three duty cycles at output currents up to 1.5 mA: (a) Group A, 7 seconds ON, 18 seconds OFF (duty cycle = 28%; $n = 19$); (b) Group B, 30 seconds ON, 30 seconds OFF (duty cycle = 50%; $n = 19$); or (c) Group C, 30 seconds ON, 3 minutes OFF (duty cycle = 14%; $n = 23$).

Preliminary data indicate that all three duty cycles are effective and well-tolerated, although side effects (primarily mild to moderate) were reported most frequently among patients in group B (30 seconds ON/30 seconds OFF, duty cycle = 50%). The percentages of patients achieving 50% or better reductions in seizure rates were similar for the three groups. However, 13% of patients in group C had seizure reductions of ≥75% versus 0% in group B and 5% in group A. Interestingly, during the first 3 months of therapy, very short duty cycles (rapid cycle) did not confer a notable benefit compared with 30 seconds ON and 3 minutes OFF. In fact, a duty cycle of 30 seconds ON and 3 minutes OFF provided seizure reductions similar to those found in the pivotal E05 trial.[3] In that trial, which led to FDA approval, the 75% responder rate for 30 seconds ON and 5 minutes OFF was 11%, similar to the 13% found for the 30-second ON and 3-minute OFF group.[3] The most important finding of the New Parameter study is that a variety of initial duty cycles are safe and effective.[27] Further analysis is necessary before definitive conclusions and recommendations can be made. Nevertheless, beginning VNS therapy with longer OFF times helps to preserve the generator battery. If the patient has shown no response after several months, then decreasing the OFF times may be appropriate.

Conclusions. The results from prospective randomized trials indicate that standard duty cycles of 30 seconds ON/5 minutes OFF, 20 to 30 Hz, at output currents from 0.25 to 3.5 mA, are safe and effective. Side effects are primarily a function of output current and, to a lesser extent, pulse duration and duty cycle. Efficacy of VNS appears to improve over the first year. This improvement may be due, at least in part, to increased output current, increased duty cycle (decreased OFF times) or, as occurs in animals, cumulative exposure.[1,2,15] Patients who do not respond to initial settings may respond to incremental increases in output current and duty cycle. Duty cycles less than or equal to 50% appear to be safe and effective.[2,16] Side effects, especially hoarseness, cough, and throat discomfort, increase as output current and duty cycle increase.[2] Side effects respond to a reduction in pulse duration (from 500 μseconds to 250 μseconds) or output current.[24,25]

Appendix 1

Suggested initial programming settings

0.25 mA output current
20 to 30 Hz frequency
250 to 500 μseconds pulse width
ON 30 seconds
OFF 5 minutes

1. Slowly titrate output current over 4 weeks to 0.50–1.50 mA, or as tolerated. If a patient cannot tolerate a given output current, first decrease current output one level. Second, reduce pulse width from 500 μseconds to 250 μseconds. Third, again try to increase output current with the reduced pulse width.
2. If a patient cannot tolerate a pulse width of 250 μseconds, reduce output current by 0.25 mA until hoarseness, cough, or throat tightness is minimized. Likewise, some patients may find adjustment of signal frequency to 20 Hz more tolerable than 30 Hz. For this reason, some physicians prefer to start at 20 Hz.
3. Keep in mind that some patients do not tolerate output currents higher than 1.0 mA. Always adjust to patient tolerance.
4. Once patients respond to VNS therapy, further increases in output current are not needed. Lower-output currents help extend the life of the generator battery. After implantation, we suggest frequent (every 2 to 4 weeks) office visits for the first several months to both track patient response and adjust device parameters. Increasing output current in increments of 0.25 mA at a time, once or twice a visit, enables the physician

to identify the settings at which changes in seizure frequency or seizure severity occur.

Adjusting duty cycle

1. After incrementally increasing the output current to 1.0 or 1.5 mA, the physician can begin adjusting the duty cycle about 3 months after implantation. In our experience, the effects of adjustments to duty cycle are apparent within 1 to 3 months, so adjustments to duty cycle should be less frequent than the initial adjustments to output current. Although some patients improve with increased duty cycle, some do not. Therefore, the patient should be closely monitored as the duty cycle is increased. Returning to more standard settings will conserve battery life for patients who have not responded to increased duty cycle after approximately 3 months.
2. After 3 months at a specific duty cycle, consider increasing the duty cycle to greater than 20% (typically, decreasing the OFF time to ≤1.1 minutes) and reevaluate for efficacy of the adjusted duty cycle after an additional 3 months.
3. As duty cycle is increased, consider reductions in output current to minimize coughing, hoarseness, and throat tightness.
4. Avoid radical changes in output current or duty cycles and allow sufficient time on a duty cycle (3 months) before changing it again, unless patient safety is an issue.

Appendix 2

Questions physicians ask

When can I safely activate the device? Guidelines in the VNS Physicians' Manual[28] suggest waiting 2 weeks after surgery before turning on the VNS. However, many physicians have developed their own approaches. No "best practice guidelines" exist, so physicians should activate the device according to the needs of the particular patient. However, many physicians activate the device at implant or shortly thereafter.

An episode of asystole, which has occurred only rarely during VNS implantation, would indicate that waiting 2 weeks before beginning VNS therapy is appropriate if VNS therapy is pursued. A particularly traumatic surgery, another rare occurrence, likewise warrants a 2-week delay. Some physicians experienced with VNS note that the patient should be able to swallow comfortably before stimulation should be turned on. Stimulation initiated soon after implantation should be kept at low settings. Otherwise, it may be difficult to distinguish between coughing caused by intubation for surgery, which is continuous, or as a side effect of stimulation, which is not continuous.

What are the most important things to remember when adjusting VNS parameters? Monitor the patient for shortness of breath, throat tightness/discomfort, excessive hoarseness, and discomfort with swallowing. Follow the guidelines in the VNS Physician's Manual[28] and use the FDA-approved settings described in section 8 of the manual. Ensure that the patient tolerates a given output current or duty cycle before allowing the patient to leave the office.

How do I manage side effects? Most side effects of VNS therapy, such as hoarseness and tightness in the neck, are fairly mild. To alleviate side effects, physicians should first try adjusting pulse width, then output current. Adjusting pulse width changes the amount of energy delivered to the vagus nerve so that the sensation is more tolerable to the patient.

What are appropriate magnet settings? Magnet settings should be programmed at 0.25 mA higher than the around-the-clock VNS therapy. Setting the output current of the magnet higher than regular VNS helps the patient become accustomed to a higher current and thereby facilitates stimulation ramp-up. Patients are instructed to swipe the magnet over the generator daily to ensure that the device is working, particularly if they do not feel it going off or have no voice change. The higher output current for the daily test enables the patient to more readily detect the sensation caused by the stimulation.

Appendix 3

Some physicians use the following progression to find the optimal duty cycles for their patients*

ON time	OFF time	Duty cycle (%)
30 seconds	5 minutes	10
30 seconds	3 minutes	16
30 seconds	1.8 minutes	25
30 seconds	1.1 minutes	35
21 seconds	0.8 minutes	36
14 seconds	0.5 minutes	41

* Duty cycle = (ON time + 4 seconds)/(ON time + OFF time), for which ON and OFF time are measured in seconds.

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Antiepileptic drug use during the first 12 months of vagus nerve stimulation therapy

A registry study

Douglas R. Labar, MD, PhD

Article abstract—Understanding interrelationships between antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS) therapy can guide research into epilepsy treatment. A constant cohort of patients with data available at baseline and 12 months were drawn from the VNS patient outcome registry and analyzed for changes in AEDs and seizure rates. Of the 1,407 patients, group 1 (n = 896) took fewer (n = 228) or the same (n = 668) AEDs at 12 months compared to baseline. Group 2 (n = 511) took additional (n = 251) or different (n = 260) AEDs. Median seizure rate reductions after 12 months of VNS therapy were 58% in group 1 and 55% in group 2. The number of and specific AEDs remained unchanged for 668 patients and dosages remained the same for 269 (40%) of these patients. The most commonly discontinued drugs were topiramate (n = 115), tiagabine (n = 78), carbamazepine (n = 62), lamotrigine (n = 56), and gabapentin (n = 52). Changes in seizure rates were not significantly different among patients who added levetiracetam (n = 151), zonisamide (n = 71), or oxcarbazepine (n = 46) to VNS. Changes in seizure rates were not significantly different among patients whose baseline AEDs were carbamazepine (n = 273), lamotrigine (n = 238), valproate (n = 201), topiramate (n = 190), or phenytoin (n = 151). Our results suggest the following: (a) patients commonly stay on the same AEDs during 12 months of treatment with VNS; (b) the registry cohort who had reduced AEDs by month 12 did not appear to experience any seizure exacerbation; and (c) no specific AED shows promise of unique additive antiepileptic effects in combination with VNS.

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The accepted sequence of medical treatment for epilepsy begins with single-drug therapy and, depending on results, can progress to polytherapy.[1,2] The decision to try a different or additional antiepileptic drug (AED) can be attributed to failure of the first drug or adverse drug side effects.[3] The severity of such side effects ranges from annoying to life threatening. Increasing the number of concurrent AEDs increases the possibility of adverse side effects.[1] After attempts to control seizures with several AEDs have failed, physicians can evaluate the patient for brain resective epilepsy surgery, try vagus nerve stimulation (VNS) therapy, or prescribe the ketogenic diet. Patients who receive VNS therapy for medically refractory seizures are usually taking two or three AEDs when VNS is initiated. Physicians discontinue, add, or switch AEDs prescribed in combination with VNS, and patients may request changes as well. Observing the relationships between AEDs and VNS and the effects of changing AEDs may aid in planning future research concerning optimal treatment combinations. This study is a pilot exploration of data from the VNS patient outcome registry. The analysis had several goals: (a) to identify combinations of AEDs and VNS with greater or lesser effectiveness in reducing seizure frequency; (b) to assess the effect of AED changes on patients' seizure rates; and (c) to describe AED treatment strategies employed by prescribing physicians during the first year of VNS therapy.

Methods. The VNS patient outcome registry was queried for a constant cohort of all patients with data available at baseline and after 12 months of VNS therapy as of September 30, 2001. The VNS registry is a database created by Cyberonics, Inc. (the manufacturer of the NeuroCybernetic Prosthesis) that enables VNS-prescribing physicians to track the progress of their patients by completing baseline clinical information forms and then submitting follow-up forms at various intervals after VNS therapy has begun. The Patient History and Implant form, submitted at baseline, collects information on patient demographics, epilepsy etiology and syndrome, historical seizure types and frequencies, and AEDs. There are no uniform required criteria for epilepsy syndrome diagnosis and classification; this information represents the treating physician's opinion. Follow-up forms at 12 months collect information on seizure types and frequencies and on AEDs for the previous 6 months. Data from the forms, submitted voluntarily by participating physicians, are compiled and maintained in the registry.

Approximately 5% of the patient history and follow-up forms arrive with missing or illegible information, and registry personnel at Cyberonics therefore query the submitting physician for clarification. Forms with unresolved

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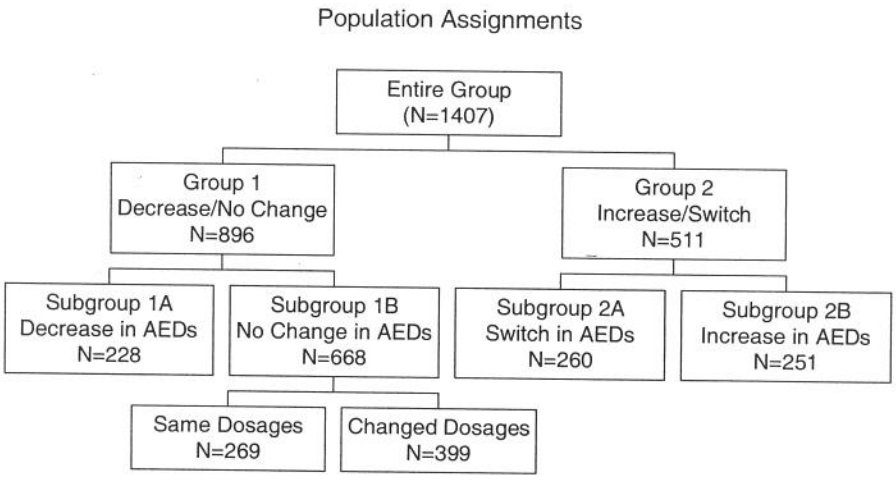

Figure 1. Population assignments.

queries are maintained apart from the registry. Once queries are resolved, the data are entered into the registry.

Patients from the constant cohort were assigned to groups according to changes in AEDs between baseline and 12 months of VNS therapy (figure 1). Group 1 comprised patients receiving fewer or the same number of AEDs at 12 months compared with baseline. Group 2 comprised patients receiving additional or different AEDs. Patients in group 1 were assigned to subgroups: subgroup 1a, consisting of patients with a decreased number of AEDs, and subgroup 1b, patients who remained on the same AEDs throughout the study. In group 2, subgroup 2a comprised patients with AEDs that were switched and subgroup 2b, patients with an increased number of AEDs.

Patients who added levetiracetam, zonisamide, or oxcarbazepine to their regimens as of the 12-month visit were analyzed separately. In addition, subgroup 1b (no change in AEDs) was further subdivided according to the specific AEDs prescribed.

Data were summarized and compared to evaluate changes in AEDs and seizure rate among patients in groups 1 and 2 and subgroups 1a, 1b, 2a, and 2b. Changes in seizure frequency were computed from the reported historical baseline and were calculated within a bounded distribution: upper and lower limits were set at −100% and 100%. Changes in AED dosing were measured in subgroup 1b. The χ^2 or Fisher's exact test was used to examine differences in binary variables between the two groups and among the four subgroups. Analysis of variance models were used to detect any differences between the two groups and among the four groups for age, age at onset, types of seizures at baseline, and total number of seizures at baseline.

Associations and differences were considered statistically significant when $p \leq 0.05$. Statistical computations for this work were performed with SAS version 8.2 (Cary, NC).

Results. Query of the VNS registry as of September 30, 2001 provided a constant cohort of 1,407 patients with data available at baseline and 12-month follow-up (figure 1). Group 1, with either decreased or unchanged AEDs, comprised 896 patients, and group 2, with either increased or switched AEDs, 511 patients.

Demographics. There were no statistically significant differences between groups 1 and 2 for epilepsy syndrome, sex (table 1), or number of AEDs at baseline. Patient total for subgroup 1a was 228 (decreased AEDs); subgroup 1b was 668 (unchanged AEDs); subgroup 2a was 260 (differ-

Table 1 *Demographics*

Group or subgroup	1	1a (decreased AEDs)	1b (same AEDs)	2	2a (switched AEDs)	2b (increased AEDs)
Demographic trait						
Baseline seizure rate (median)	24*	30	21	32*	33	32
Age (mean years)	28.7*	25.0	30†	25.3*	24.9	25.7
Epilepsy syndrome						
Partial (%)	62	60	63	59	59	59
Generalized (%)	36	36	35	38	37	39
Unclassified (%)	2	4	2	3	4	2
Male	480	129	351	261	127	134
Female	416	99	317	250	133	117
Age at onset (mean years)	7.6	5.3†	8.4	7.6	7.0	8.3

* Statistically significant difference between groups 1 and 2 ($p \leq 0.05$).
† Statistically significant difference between subgroups 1a, 1b, 2a, and 2b ($p \leq 0.05$).

Table 2 *Top AEDs at baseline by group*

All Patients			
AED	*n* at baseline	*n* continuing at 12 months*	% continuing
Carbamazepine	508	446	88%
Lamotrigine	475	419	88%
Topiramate	444	328	74%
Valproate	436	397	91%
Phenytoin	341	299	88%

Group 1 (AED Decrease/No Change)			
AED	*n* at baseline	*n* at 12 months*	% continuing
Carbamazepine	360	343	95%
Lamotrigine	325	299	92%
Topiramate	284	234	82%
Valproate	283	270	95%
Phenytoin	204	196	96%

Group 2 (AED Increase/Switch)				
AED	*n* at baseline	*n* continuing at 12 months*	% continuing*	*n* adding AED by 12 months
Carbamazepine	148	103	70%	25
Lamotrigine	150	120	80%	36
Topiramate	160	95	59%	41
Valproate	153	127	83%	29
Phenytoin	137	103	75%	18

* Of the patients who were taking the AED at baseline, these patients continued to take it at 12 months.

ent AEDs); and subgroup 2b was 251 (increased AEDs). Group 1 had a lower baseline seizure rate (median 24 seizures per month) than did group 2 (median 32 seizures per month). Group 1b was older than the other groups. Group 1a had a younger age of epilepsy onset than the other groups.

AEDs. At baseline, carbamazepine, lamotrigine, topiramate, valproate, and phenytoin were the most frequently prescribed AEDs for both groups. Table 2 lists the AEDs and their continuation rates for all patients at 12 months. Most patients were receiving multiple AEDs. Patients receiving topiramate at baseline were less likely to remain on it at 12 months' follow-up than those starting on the other four most common AEDs.

Seizure rate changes. All patients. For group 1, physicians reported a median seizure reduction of 58% after 12 months of VNS. The median seizure reduction in group 2 was similar, 55% after 12 months. Figure 2 shows the percentage of patients with seizure reductions ≥50%, ≥75%, ≥90%, and 100% (seizure-free) for both groups 1 and 2. Figure 3 shows the percentage of patients with seizure reductions of ≥50%, ≥75%, and ≥90% for the four subgroups. There were no significant differences in seizure rate changes among the groups and subgroups.

Drug additions. Of patients in subgroup 2a, who switched AEDs, and subgroup 2b, who added AEDs, (total $n = 511$), the most commonly added AEDs during the first year of VNS therapy were levetiracetam ($n = 151$ of 511, 30%), zonisamide ($n = 71$, 14%), and oxcarbazepine ($n = 46$, 9%). The median seizure reductions for patients adding each of these AEDs at 12 months were 56% (levetiracetam), 50% (zonisamide), and 55% (oxcarbazepine), which were not statistically different from the 12-month seizure rate reductions among the patients who did not add the specified AED (figure 4). At 12 months, the median number of AEDs remained at two for group 1 but increased to three for group 2, which was significantly different ($p < 0.001$).

Drug discontinuations. The most commonly discontinued drugs were topiramate, discontinued by 115 of 444 patients (26%) taking it at baseline; tiagabine, 78 of 198 (39%); carbamazepine, 62 of 508 (12%); lamotrigine, 56 of 475 (12%); and gabapentin, 52 of 178 (29%). Among the 228 patients in subgroup 1a, who discontinued at least one AED but did not add any other AEDs by 12 months, the most commonly discontinued AEDs were topiramate, discontinued by 50 of 94 patients (53%) taking it at baseline; gabapentin, 27 of 44 (61%); tiagabine, 26 of 36 (72%); and lamotrigine, 26 of 87 (30%). Some patients discontinued more than one AED and were therefore counted in different categories. At 12 months, the overall median seizure decrease in subgroup 1a was 62% compared with 52% among patients in subgroup 2b whose AEDs were increased (NS).

Median seizure reductions of patients in subgroup 1a (who decreased the number of AEDs) at 12 months were 75% for the 50 patients stopping topiramate, 55% for the 27 patients stopping gabapentin, 44% for the 26 patients stopping tiagabine, and 74% for the 26 patients stopping lamotrigine (figure 5). Median seizure rate reductions were significantly greater ($p = 0.047$) among patients in subgroup 1a who discontinued topiramate compared with other patients in subgroup 1a who remained on topiramate throughout the 12 months.

Dosing changes. The number of and the specific AEDs remained unchanged for the 668 patients in subgroup 1b. Of this subgroup, 269 patients (40%) remained on exactly the same dosages of their AEDs throughout the year of the

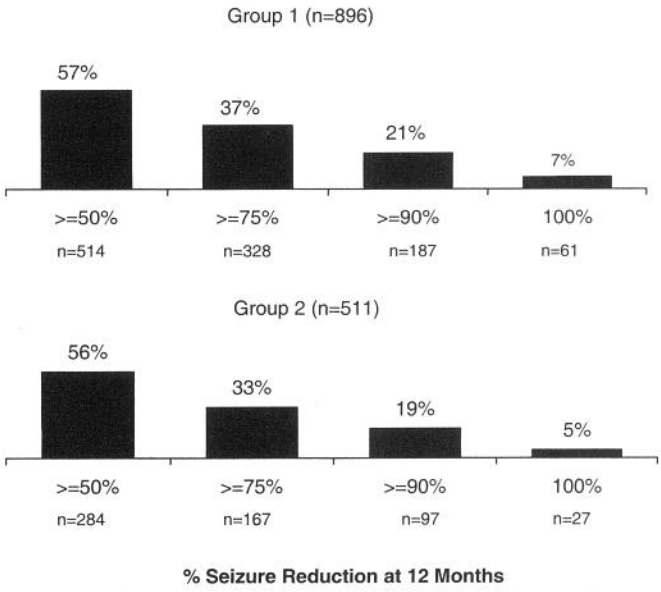

Figure 2. Seizure reductions for groups 1 and 2 at 12 months.

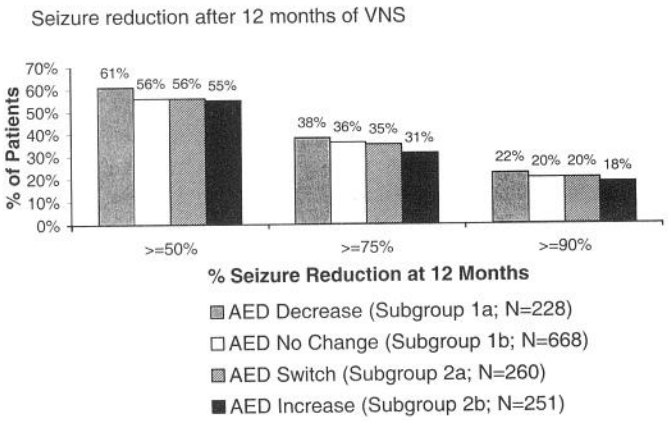

Figure 3. Percentage seizure rate reductions for subgroups at 12 months.

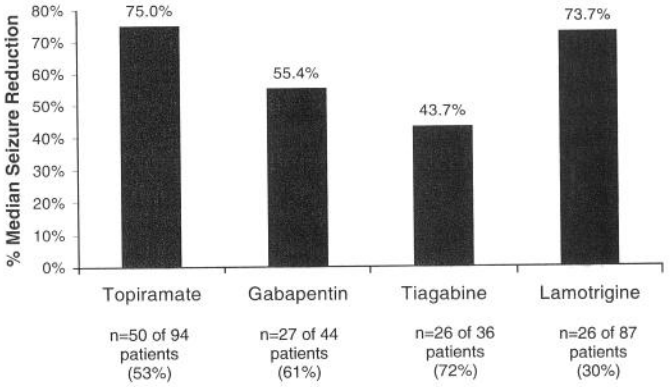

Figure 5. Median seizure rate reductions at 12 months of patients discontinuing topiramate, gabapentin, tiagabine, and lamotrigine.

analysis. Median seizure rate decrease among these 269 patients was 58% at 12-month follow-up compared with 56% among the other 399 patients in subgroup 1b and 56% among the other 1,138 patients in the study group. The medications prescribed most commonly for the 668 patients in subgroup 1b, who did not change their AEDs, were carbamazepine (n = 273), lamotrigine (n = 238), valproate (n = 201), topiramate (n = 190), and phenytoin (n = 151). The median seizure rate reduction at 12 months was 53% for patients remaining on carbamazepine, 54% for patients remaining on lamotrigine, 62% for patients remaining on valproate, 56% for patients remaining on topiramate, and 56% for patients remaining on phenytoin (figure 6).

Discussion. *Registry methodology and patient selection bias.* Data for this analysis came from the VNS patient outcome registry. Ratings of strength of evidence traditionally place analyses from registries between case series with controls from the literature and case-control observational studies.[4] At present, approximately 16,000 patients have been treated with VNS and 6,000 patients have been enrolled in the registry.

Participation in the outcome registry is voluntary. Therefore, some epilepsy centers and some physician practices do not enroll their implanted patients. Even within a center or physician's practice, registration of patients may be selective and could be biased by changes in seizure frequency or number of AEDs, age, etiology, developmental disability, payer class, or when the patient was implanted. Approximately one in 20 patient history and follow-up forms arrives with missing data. All of these factors may produce patient selection bias. Furthermore, the patient history forms do not provide specific criteria for diagnosis and seizure classification, and interpretation of the history and symptoms is therefore at the discretion of the physician submitting the information. The registry may draw strength, however, from the large numbers of patients and submitting physicians. Whereas observations from a single investigator might reflect that individual's bias, the diversity represented in the registry may be an advantage.

An attempt was made to minimize the effect of patient selection bias by posing research questions comparing subgroups of patients *within* the registry population rather than about the registry population in general. For example, physicians at one hospital may register more of their VNS therapy patients than do physicians at another hospital. However, within each group of registered patients, there is no reason to suspect that patients receiving VNS therapy plus one AED were reported differently than

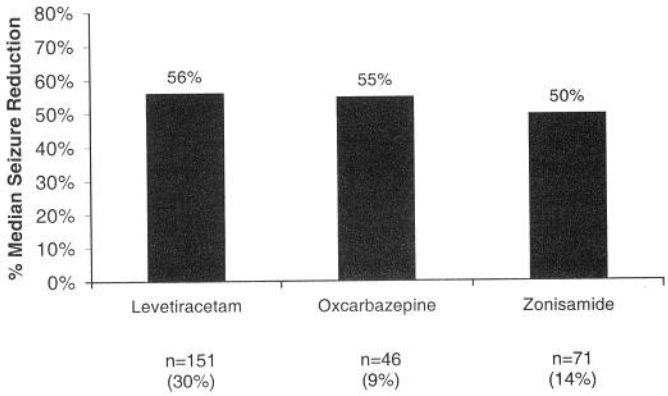

Figure 4. Median seizure rate reductions at 12 months for patients in subgroup 1a adding levetiracetam, zonisamide, or oxcarbazepine (percentages were calculated from the 511 patients who added or switched AEDs).

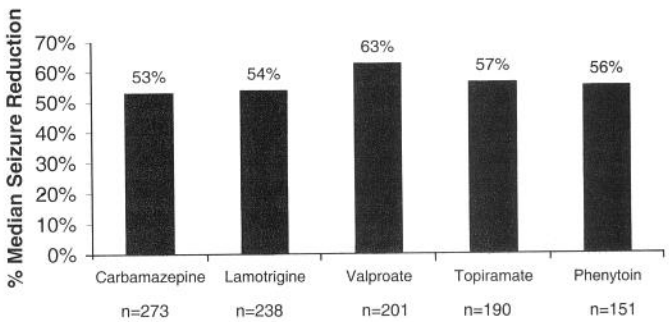

Figure 6. Median seizure rate reductions at 12 months for patients in subgroup 1b who remained on AEDs and had no dosage changes throughout the year of the analysis.

were patients receiving VNS therapy plus some other AED. Furthermore, observations that applied only to the registry population were not generalized to *all* patients treated with VNS.

A major limitation of this study is that the registry was queried retrospectively. Consequently, information was gathered before research questions were posed. One potential consequence of retrospective analyses is that additional information that might be helpful in drawing conclusions may not be available. For example, the VNS registry patient history and follow-up forms do not gather information on the rationale for changes in AEDs or AED dosing, or on any adverse effects of VNS therapy or AEDs. Because VNS therapy is delivered automatically, compliance with therapy is not an issue. On the other hand, AED information in the registry is limited to AEDs and dose as prescribed, not necessarily as taken. Given these and other limitations, this analysis must be considered exploratory. Nevertheless, this analysis yielded several results that warrant comment.

Seizure rates. In this analysis, the number of AEDs prescribed was reduced by one or more medications for 228 of 1,407 VNS-treated patients by 12 months' follow-up. In that group, at that follow-up interval, 61% of patients had seizure rate reductions of 50% or greater. It can be hypothesized that the antiepileptic effects attributable to the introduction of VNS therapy may have allowed this AED withdrawal. On the other hand, perhaps the withdrawn AEDs were ineffective and might have been withdrawn anyway, even in the absence of VNS therapy. However, that would not explain the degree of seizure rate reduction seen in this group, which would not be expected to occur as part of the natural history of medication-resistant epilepsy. It is possible that the AEDs that were removed may have iatrogenically exacerbated seizures. Finally, seizure improvement could reflect the natural history of epilepsy in some patients or could be the result of changes in lifestyle. Nevertheless, these results do suggest that, in a substantial fraction of VNS-treated patients, one or more AEDs can be withdrawn without a "rebound" increase in the seizure rates. However, these patients cannot be identified in advance.

Patients with increased or switched AEDs (group 2) had a higher baseline seizure rate than did patients with decreased or unchanged AEDs (group 1). It is likely the more frequent seizures experienced by group 2 patients prompted the treating physicians to modify the AED regimen and to be less likely to recommend decreasing the number of AEDs. Perhaps if patients with lower baseline seizure rates had also had new AEDs added to VNS therapy, additive antiepileptic effects with VNS therapy might have been seen.

AEDs administered with VNS therapy. During the VNS therapy clinical trials, patients were maintained on the AEDs that they were receiving at implantation unless they experienced adverse events.[5] This measure helped avoid confounding the results of the studies. Almost half (668 of 1,407) of the patients in our current analysis remained on the same AEDs throughout the 12 months of the study. Considering that VNS therapy is still a relatively new therapy, having been approved by the FDA only 5 years ago, many clinicians might be trying to emulate the conditions of the clinical trials. Tatum et al.[6] reported reductions in AED usage or dosage among 16 of 21 patients during the mean 13.2 months after they began VNS therapy. They compared the VNS therapy patients with a case-matched control group of patients with refractory epilepsy who were receiving AEDs and found AED reductions among the VNS therapy patients to be significantly greater.

Although patients with AEDs switched or added (group 2) had the same seizure rate reductions as those receiving the same or fewer AEDs (group 1), one cannot conclude that switching or adding AEDs had no effect on these group 2 patients. Perhaps the patients in group 2 would have done worse than those in group 1 if AEDs had not been switched or added. In addition, AEDs could have been switched to minimize side effects. Group 2 also was slightly younger than group 1, which may indicate that pediatric neurologists and parents of children with epilepsy may be more likely to reduce dosages or numbers of AEDs than adult neurologists. The constant cohort analysis provided seizure rates at only baseline and at 1-year follow-up. No interim data were available for analysis, including the relative timing of changes in seizure frequency and AEDs.

The relationship of VNS therapy and AEDs offers many avenues for exploration and investigation. This study focused on AED changes in patients whose seizure rates were reduced. However, future studies can broaden the approach and focus on other changes or patient demographics. For example, an investigation of patients whose seizure rates increased may provide additional insight into the VNS–AED relationship and whether a particular AED is associated with increased seizure rate. Another possibility is subdividing the study groups according to seizure syndrome, e.g., partial versus generalized, which may reveal greater efficacy of VNS therapy and a particular AED in treating a certain epilepsy syndrome. Such possibilities warrant exploration, and the results may be useful in delineating the VNS–AED relationship.

The mechanism of the antiepileptic action of VNS therapy is unknown. Contributions from central noradrenergic and serotonergic systems have been proposed.[7,8] It is not unreasonable to consider that the VNS mechanisms of action might be complementary to the mechanisms of action of one AED or another or perhaps to a non-AED that modulates noradrenergic or serotonergic function. However, our pilot exploration of the VNS registry data failed to yield any suggestion that any one AED is particularly complementary to VNS therapy, either when VNS therapy is added to a stable, unchanged baseline AED or

when a new AED is added after VNS therapy has been established.

Conclusions. Our results suggest the following: (a) patients commonly stay on the same AEDs during 12 months of treatment with VNS; (b) the registry cohort that had reduced AEDs by month 12 did not appear to experience any seizure exacerbation; and (c) no specific AED shows promise of unique additive antiepileptic effects in combination with VNS therapy.

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Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients

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Article abstract—Vagus nerve stimulation (VNS) therapy is an established method for treating patients with refractory seizures. Although the initial cost of the device is about $10,000, the battery life of the model 100 implanted in the patients in this analysis can exceed 5 years at standard settings. It is important to understand what type of cost–benefit can be expected after implantation. Our aim was to assess unplanned hospital costs 18 months before and 18 months after VNS implantation in 43 patients. The VNS therapy system was implanted according to standard procedures and stimulation of 0.75 to 2.0 mA was delivered either as 30 seconds on and 5 minutes off or 7 seconds on and 14 seconds off. Seizure frequency was calculated before and after 18 months of treatment. During this time no changes were made with other therapies for epilepsy. Hospitalization for emergency room (ER) visits, ward stays, and intensive care days were calculated according to the costs at Sahlgrenska University Hospital in Sweden. Therapy response was defined as 25% or greater reduction in seizure frequency. For all patients, intensive care unit (ICU) costs were reduced from $46,875 to $0, ER visits from $13,000 to $9,000, and ward stays from $151,125 to $21,375. Total hospital costs for the 43 patients studied before VNS therapy were $211,000 and after 18 months of treatment were reduced to $30,375, an average annual cost savings of approximately $3,000 per patient. The cost savings applied to all patients, irrespective of whether they responded to VNS therapy. VNS therapy resulted in annual reductions of approximately $3000 in unplanned hospital costs per study patient. Such direct savings sustained over the battery life of the VNS therapy system can equal or exceed the purchase price of the device.

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Vagus nerve stimulation (VNS) therapy is approved and recognized for the treatment of refractory epilepsy. The VNS therapy system from Cyberonics (Houston, TX) has been approved for use in the United States, Canada, Europe, and other areas of the world. Registration has been based on the results of two double-blind controlled studies involving 367 patients with refractory partial seizures.[1-3] The cost of the VNS therapy system, device Model 100 and lead mode 300-20, as used in this study, was about US $10,000 in 1999. Hospital costs, surgeon fees, cost of anesthetic, and other costs associated with implantation vary but can reach $5,000 or more. In addition, at the beginning of VNS therapy, the patient will probably visit the physician's office for device programming more frequently than a patient treated only with antiepileptic drugs (AEDs). The battery life of the VNS therapy Model 100, which was implanted in the patients in this analysis, varies with parameter settings. If the Model 100, serial numbers above 10,000, is operated up to 2 mA output current, 30 Hz frequency, 500 μsecond pulse width, standard impedance, and a duty cycle of 30 seconds on and 5 minutes off, the battery can be expected to last for more than 5 years at standard settings. The battery of the newer Model 101, priced similarly to the Model 100, is expected to last for 8 to 10 years.

Does VNS therapy offer any benefits in reducing the direct cost of patient care? Given the high cost of developing new technologies and drugs and the diminishing cash resources for healthcare, this is an important question. We followed the direct healthcare costs of 43 patients at 18 months before and 18 months after implantation of the VNS device and evaluated the number of unplanned visits to the medical, surgery, or neurology ward, emergency room (ER), and intensive care unit (ICU) that were attributed to epilepsy, treatment of emergent side effects, or injuries due to seizures. Our evaluation was focused on comparing unplanned health-care costs before and after implantation with the VNS therapy system.

Methods. This study involved a retrospective medical record review to obtain background information before implantation of the VNS therapy system and a prospective, open long-term follow-up evaluation of 43 patients receiving VNS therapy at the Department of Clinical Neurosciences, Sahlgrenska University Hospital, Göteborg University. The patients had partial seizures (n = 34),

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primarily generalized seizures ($n = 3$), or Lennox–Gastaut Syndrome (LGS) ($n = 6$). The patients' seizures were pharmacoresistant to available AEDs and many patients had failed epilepsy surgery. At the time of VNS therapy system implantation, all patients were being treated with one to four AEDs. The dosage of the AEDs was not changed during the first 18 months of VNS therapy except for dose adjustments due to AED side effects.

The complete patient records were obtained retrospectively for the 18 months before implantation. Patient records were then prospectively followed for 18 months. Most often, patient diaries were available for the full 18 months before treatment and all patients kept seizure diaries after implantation.

Estimated medical costs. Medical cost estimates in 1999 were one ER visit $500, one day on a ward $375, and one day in the ICU $1,875. These cost estimates were obtained from the financial officer of the Neurology Department at Sahlgrenska University Hospital. The goal of the study was to compare hospital admissions costs directly associated with epilepsy and injuries that patients might sustain as a result of uncontrolled seizures. Therefore, some costs were not included in the analysis: assessment for epilepsy surgery, the purchase of the VNS therapy system and the implantation procedure, costs for office visits to adjust device parameters, outpatient laboratory analyses, and AEDs.

Implantation operation. The VNS therapy generator was implanted in the upper left chest with the stimulating lead attached to the left vagus nerve in the neck. The generator itself is 55 millimeters in diameter, 13.2 millimeters in height, and weighs approximately 55 grams. The lead is 43 centimeters long and 2.0 millimeters in diameter. The implantation procedure takes 1 to 2 hours. Once implanted, the generator can be programmed externally with a programming wand attached to a standard personal computer. Frequency, output current, pulse width, signal on time, signal off time, and magnet parameters are then adjusted by using the programming system.

Programming of the VNS therapy system. The pulse generator ramping up process was done on an individualized basis. If the patient was not affected directly postoperatively, the stimulation was started at 0.25 mA 2 days after implantation. Otherwise, the first ramp-up adjustment was done when the sutures were removed 10 days after the operation.

After the first ramp-up visit, patients returned every other week for increases in the current until an output current of 1.0 to 1.25 mA was reached. Follow-up visits were scheduled every 3 months to assess efficacy and make parameter adjustments. Patients began with standard stimulation intervals of 30 seconds on and 5 minutes off. If good seizure control was not obtained or if the patient complained of hoarseness, rapid stimulation of 7 seconds on and 0.2 minutes off was tried for at least 3 months to evaluate efficacy.

Efficacy. The reduction of seizure frequency was calculated from patient diaries and patient records as the percent change in seizure rates during the past 3 months (months 16 through 18) of VNS compared with the seizure rates 3 months before implantation. For the purposes of this study, response to therapy was defined as a seizure reduction of 25% or greater.

Results. *Patient demographics.* Cost benefit data were available for 43 patients (24 males and 19 females). In 1999, when these data were collected, the average patient age was 38.7 years. Age at onset, available for 42 of the 43 patients, averaged 12 years. At baseline, the median number of seizures, available for 40 patients, was 18 per month (range 3 to more than 2,000).

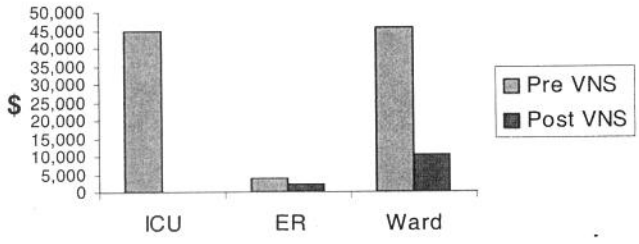
General considerations. The range of VNS stimulation was between 0.25 and 2.0 mA. The magnet function was always set at one magnitude higher than the chronic stimulation. Thus, if the chronic intermittent stimulation were 0.75 mA, then the magnet stimulation would be set at 1.0 mA.

Overall efficacy. Of 43 patients, 15 had less than 25% reductions in seizure frequency and 28 had 25% or greater reductions in seizure frequency.

Patients with less than 25% seizure rate reduction. This patient group did not experience a marked reduction of seizures after 18 months of VNS therapy. Seizure severity was not analyzed systematically and it is therefore difficult to estimate whether seizure severity was reduced

Table *Number of hospital admissions for patients treated with VNS therapy from 18 months before through 18 months after implantation*

	Number of patients	Number of hospital admissions					
		ICU admissions		ER visits		Ward admissions	
		Before VNS	After VNS	Before VNS	After VNS	Before VNS	After VNS
<25% seizure reduction	15	6	0	8	4	16	5
		(24 days)	(0 days)			(122 days)	(28 days)
≥25% seizure reduction	28	1	0	18	13	32	7
		(1 day)	(0 days)	(18 days)	(14 days)	(281 days)	(29 days)
Partial seizures	34	6	0	20	13	38	10
		(15 days)	(0 days)	(20 days)	(16 days)	(301 days)	(52 days)
Lennox–Gastaut syndrome	6	1	0	3	3	4	2
		(10 days)	(0 days)	(3 days)	(0 days)	(52 days)	(5 days)
Idiopathic Generalized seizures	3	0	0	3	1	6	0
		(0 days)	(0 days)	(3 days)	(2 days)	(50 days)	(0 days)



Intensive care unit (ICU), Emergency room (ER),

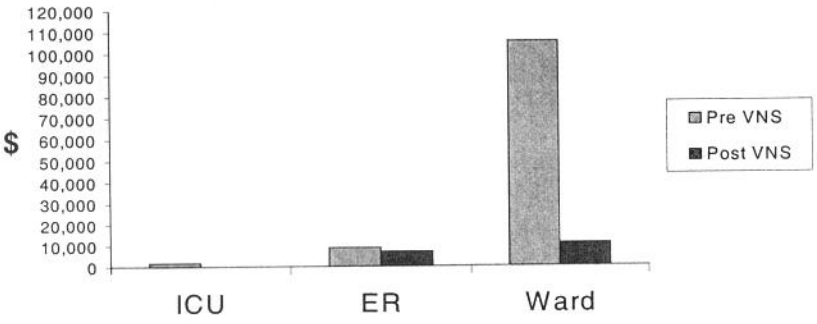
Figure 1. Hospital costs of nonresponding patients from 18 months before through 18 months after implantation with the VNS therapy system.

without an accompanying reduction in seizure frequency. Still, ICU admissions were reduced from six admissions to zero, and mean days in the ICU were reduced from 24 to 0. Visits to the ER were reduced by 50% from eight to four and ward admissions from 16 to five. Ward days were reduced from 122 days to 28 (table). Total ICU costs were $45,000 before VNS therapy and $0 afterwards. Costs for the ER were $4,000 before and $2,000 after. Ward days cost $45,750 before and $10,500 after VNS therapy (figure 1).

Patients with 25% or greater seizure rate reduction. Patients who experienced a 25% or greater seizure rate reduction had results similar to the patients in the nonresponder group. Only one person had been admitted to the ICU before implantation and none afterward. Visits to the ER were marginally reduced from 18 to 13 and ward visits were reduced from 32 to 7. Only 1 day was spent in the ICU before and 0 after VNS therapy. There were 18 days at the ER before and 14 after. Ward days were 281 before and only 29 afterwards (table). Costs for the ICU were $1,875 before and $0 after. Visits to the ER cost $9,000 before and $7,000 after, and costs for ward visits were reduced from $105,375 to $10,875 (figure 2).

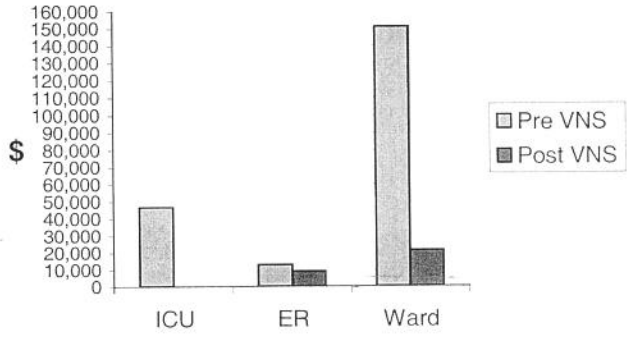
Costs according to seizure type. Patients with partial seizures. Thirty-four patients had partial seizures. Admissions before VNS therapy were six for ICU, 20 for ER, and 38 for ward. After VNS therapy, ICU visits were zero, ER were 13, and ward 10. Days spent in hospital before VNS therapy were ICU 15, ER 20, and ward 301. After implantation, there were 0 ICU days, 16 ER, and 52 ward days.

Patients with Lennox–Gastaut syndrome. Six patients with Lennox-Gastaut Syndrome were studied. Before implantation, the ICU visits numbered one, the ER three, and ward admissions four. After VNS therapy there were no ICU visits, three ER, and two ward visits. Before VNS therapy, days in the hospital were 10 for ICU, 3 for the ER, and 52 for the ward. After implantation, hospital days were 0 for the ICU, 0 for the ER, and 5 for the ward.



Intensive care unit (ICU), Emergency room (ER)

Figure 2. Hospital costs of patients with ≥25% seizure reduction from 18 months before through 18 months after implantation with the VNS therapy system.



Intensive care unit (ICU), Emergency room (ER),

Figure 3. Total costs for the entire patient population 18 months before and 18 months after VNS therapy.

Patients with idiopathic generalized seizures. The three patients with idiopathic generalized seizures had no ICU visits during either period, three ER visits before implantation and one after, and six ward admissions before and none after. The days in hospital were 0 for the ICU, 3 for the ER before and 2 after, and 50 ward days before and 0 after.

Total costs for all patients combined. For all patients, responders and nonresponders alike, ICU costs were reduced from $46,875 to $0, ER visits from $13,000 to $9,000, and ward stays from $151,125 to $21,375 (figure 3). Total hospital costs for the 43 patients studied before VNS therapy were $211,000 and after 18 months of treatment were reduced to $30,375, an average annual cost savings of approximately $3,000 per patient.

Discussion. Epilepsy is an expensive illness. The cost of treating refractory epilepsy in the United States before 1994 was estimated between $1,169 and $7,717 annually.[1] The analysis did not involve estimating indirect costs but focused on the costs that are important to health-care providers in deciding what therapies can be offered to patients. In another more recent study, Begley et al.[2] found that indirect costs account for 85% and that the direct costs were mostly seen in patients with intractable epilepsy, the population addressed in the present study (the costs for implantation of the VNS therapy system are not included in our study). Important

factors for direct costs for our patients appear to be the actual costs for the hospital, such as days on the ward and the costs involved therein. This prospective study showed that VNS therapy can decrease hospital costs of refractory epilepsy. This savings might be attributable to the decrease in seizure severity for up to 18 months after implantation, even in patients with less than 25% seizure reductions. Considering the hospital costs usually incurred by patients with refractory epilepsy, and assuming that hospital admissions remained or were less than those for the first 18 months after implantation, the results of this study show that the purchase price of the VNS therapy system can be absorbed within 2 to 3 years. The Model 101, introduced since this analysis began, has an estimated battery life of 8 to 10 years. Therefore, the cost of VNS therapy would be much less than that of using a new AED (estimated at $2,000 per year) over the same time frame. VNS therefore ends up being a comparatively inexpensive therapy.[4]

Treatment records for our patient group were readily available, and it is unlikely that a ward admission was not recorded. Because the AEDs were not changed during the observation time, their costs were not included in the analysis. Patients in the ICU received multiple medications, but these were included in the estimated daily charges. Therefore, the calculations very closely reflect the actual costs of an emergency visit, ward day, or ICU day in this particular health-care system.

Clinically significant seizure reduction is usually defined as a greater than 50% reduction of seizures.[5] However, in this analysis responders were classified as those with seizure reductions of 25% or more. We have empirically found that many patients with 25% to 40% seizure reductions do, in fact, consider themselves to be helped by VNS therapy (or by any newly added treatment, for that matter). Therefore, we set broader criteria for therapy response so that we could more clearly identify patients who did not benefit from VNS therapy. Before implantation, hospital costs totaled $6,317 per nonresponding patient and $4,152 per responding patient. These larger hospital expenditures may reflect a greater severity of seizures among the nonresponders. To our surprise, hospital admissions and days were decreased even among the patients with less than 25% seizure reductions.

This study has several limitations. First, it compares only costs of unplanned hospital admissions directly associated with epilepsy and injuries that patients might sustain as a result of uncontrolled seizures. Indirect costs to society, such as lost workdays or disability payments, were not considered. In addition, assessment for epilepsy surgery, the purchase of the VNS therapy system and the implantation procedure, costs for office visits to adjust device parameters, and AEDs were not included in the comparison. Second, the costs used in the comparison are estimates. Although the estimates allowed for medications in addition to hospitalization costs, the totals are not exact. Third, data were available for 18 months after implantation, which does not allow sufficient time for the computed savings to equal costs associated with VNS therapy. Therefore, savings are projected on the assumption that admissions will remain steady or decline until enough time has passed for savings to exceed costs.

Epilepsy profoundly affects the lives of the sufferers. It is encouraging that VNS therapy has the capability of relieving some of the health-care burden by reducing hospital admissions among patients who experience a significant reduction of seizure frequency. Even more encouraging were the reduced costs for patients whose seizure frequency was reduced less than 25%. From a financial standpoint, VNS therapy was able to reduce the economic burden for both patients in our study and society as a whole.

The efficacy of VNS therapy increases with time, with maximal effect at 18 to 24 months.[6] Because the present study collected information from the first day of stimulation through the 18-month cut-off point, it is noteworthy that ICU and ward admissions decreased from the very start of VNS therapy, irrespective of an overt decrease in the number of seizures. This promising information can be of importance to patients and health-care providers who desire rapid benefits.

Acknowledgments

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The co-morbidity of depression and epilepsy

Epidemiology, etiology, and treatment

Cynthia L. Harden, MD

Article abstract—Co-morbid depression is common in patients with epilepsy and is often undiagnosed. The manifestation of depression in epilepsy is multifaceted with many interacting neurobiological and psychosocial determinants, including clinical features of epilepsy (seizure frequency, type, foci, or lateralization of foci) and neurochemical or iatrogenic mechanisms. Depression is reported more frequently in patients with temporal lobe epilepsy (TLE) and left-sided foci, although not all studies support this finding. In patients with depression and epilepsy, optimal control of seizures should be attained first and foremost with appropriate anticonvulsant treatments including antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS) therapy. Some anticonvulsant treatments (VNS, valproate, carbamazepine, lamotrigine, and gabapentin) have demonstrated mood improvement in epilepsy patients and may have therapeutic potential for this patient population. When antidepressants are necessary to treat depression in patients with epilepsy, selective serotonin reuptake inhibitors (SSRIs) and multireceptor antidepressants are considered first-line treatments. Electroconvulsive therapy is not contraindicated for treatment-resistant or psychotic depression. Depression must be recognized, diagnosed, and adequately treated in patients with epilepsy.

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Symptoms of depression and anxiety are common and under-recognized in patients with epilepsy.[1,2] On the basis of studies utilizing self-reporting scales, up to one-half of patients have clinically significant anxiety and/or depression. However, general practitioners only detect one-third of these patients.[3] The causes of depression in patients with epilepsy are probably multifactorial, including clinical (seizure frequency, seizure type or foci, epilepsy duration, age at onset) and psychosocial factors (quality of life, life stressors, employment, marital status).[4-6] Clinical or psychosocial factors cannot fully account for the high prevalence of depression in patients with epilepsy because the biological characteristics of epilepsy also affect the manifestation of depression.[7,8] Furthermore, major depression is associated with a six-fold increased risk for the development of unprovoked seizures.[9]

Interictal depression. *Epidemiology.* Depression is more common and severe in patients with epilepsy than patients with other chronic medical or neurologic conditions.[10,11] The prevalence of depression is much higher in patients with epilepsy than in the general population (2% to 9% for women; 1% to 3% for men).[12,13] Community-based studies of epilepsy populations report rates of depression from 9% to 22%.[6,14,15] Hospital-based samples generally report higher rates of depression (27% to 58%) for patients with epilepsy or medically refractory epilepsy.[16-18]

Etiology of depression in epilepsy. *Gender and genetic factors.* Although the literature remains inconclusive, most epilepsy studies report men to be at higher risk than women for the development of depression.[10,19] Altshuler et al.[20] reported the interesting finding that the combination of left temporal lobe epilepsy (TLE) interacted with male gender to increase the risk of depression.

Genetic factors may also play a role in the co-morbidity of epilepsy and depression. In one study, more than 50% of patients (n = 66) with both epilepsy and depression had a family history of psychiatric illness, most often depression.[1] Other reports do not support these findings.[10,17,21] Whether the genetic influence predisposing epilepsy patients to depression is greater than in the general population, however, remains an unresolved issue.

Clinical characteristics. *Age at onset, duration, and seizure frequency.* Most studies report no association between depression and age at onset of epilepsy[15,17,22] or duration of epilepsy.[17,21]

It is postulated that seizures may be a form of electroconvulsive therapy in some patients, and may therefore have an antidepressive effect. Decreased seizure frequency has been reported before the onset of depression in epilepsy patients.[1] Furthermore, Mendez et al.[11] reported that patients with epilepsy and depression had fewer generalized tonic–clonic seizures than epilepsy patients without depression.

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Depression in these patients may be an example of forced normalization, which is the term used to describe exacerbation of psychiatric illness, specifically depression or psychosis, as seizure frequency improves. Forced normalization was first described by Landolt[23] in 1953 and in 1958 was termed as such.[24] Landolt[23,24] postulated that forced normalization was due to an excess of generalized electrophysiologic inhibition after a seizure, although the exact mechanism and its relationship to the risk for depression are unclear. Blumer et al.[25] described seven patients who received vagus nerve stimulation (VNS) therapy and developed major psychiatric disorders after their seizures were decreased by 75% or more. All seven had dysphoric disorders before treatment with VNS.

Seizure type and localization of focus. Depression is reported more frequently in patients with complex partial seizures[10,21,26,27] and temporal lobe foci than in patients with generalized epilepsy or extratemporal foci.[10,27-29] Lifetime prevalence for depression of 39% was reported in patients with medically refractory complex partial seizures with localized onset in the temporal lobe.[30] Similar rates of depression and anxiety are reported in patients with temporal lobe and other epilepsies.[22,31] However, Manchanda et al.[32] assessed patients with TLE, nontemporal lobe focal epilepsy, or multifocal onset/generalized epilepsy, and found no significant difference in psychiatric morbidity among the different foci.

An explanation for these inconsistencies may be that frontal lobe dysfunction is a necessary component for the development of depression in TLE patients, as suggested by the findings of a bilateral reduction in inferior frontal lobe glucose metabolism on PET scans in patients with depression and TLE.[33] Given the widespread afferent input into frontal regions, dysfunction in the temporal lobe due to an epileptic focus may result in hypometabolism of extratemporal regions (e.g., frontal lobe and thalamic regions), increasing the vulnerability to depression.[31] Moreover, Victoroff et al.[18] reported that the combination of interictal left temporal lobe hypometabolism and "high-degree" hypometabolism was significantly associated with major depression.

The precise localization of the temporal lobe epileptogenic lesion in the temporal lobe may also be a determinant of depression in patients with epilepsy. Patients with mesial-temporal sclerosis (MTS) show significantly higher depression scores ($p = 0.004$) than patients with neocortical temporal lesions (NTLs), independent of the lateralization of the epileptic lesion.[34]

Lateralization of seizure focus. Although higher lifetime rates of depression have been reported among patients with left TLE,[11,19,20] several authors have found lateralization not to be a major factor.[21,32,35] Given these discrepancies, the issue of increased risk for depression in left-sided TLE remains unresolved.

In patients with left TLE, a significant correlation ($p < 0.05$) was found between a self-reported dysphoric mood state and the degree of frontal lobe dysfunction.[36,37] Furthermore, reduced activity measured with SPECT in bilateral frontal and right temporal regions was associated with higher scores on the Beck Depression Index (BDI) in patients with left-sided TLE.[38] These findings also suggest an association between frontal lobe dysfunction and depression in patients with TLE, most likely those with left-sided foci. The hypoperfusion (hypometabolism) observed in the limbic frontal regions in patients with TLE may be related to interictal inhibitory activity, postictal depletion of substrates (decreased levels of neurotransmitters), or functional deafferentation.[33]

Psychoactive effects of AEDs. The behavioral effects of AEDs vary with the particular drug. Among adults, barbiturates have been more closely linked to depression than other frequently prescribed AEDs, and they have been associated with depression and suicidal ideation among children.[39,40] Psychiatric interviews of children with epilepsy who were managed with carbamazepine or phenobarbital revealed major depression among 40% of those receiving phenobarbital compared with 4% of those receiving carbamazepine.[39]

Over half the studies discussed in a 1991 review of AEDs available at the time found that carbamazepine and valproate elevated mood.[41] The same review listed equal numbers of reports of positive and negative mood effects of phenytoin and provided support for the strong association of barbiturates with negative mood changes.[41] Both valproate and carbamazepine, well-acknowledged for their mood-stabilizing effects, have become standard treatments for bipolar disorder.

Negative mood changes associated with vigabatrin are supported in the Marion Merrell Dow Global Safety Data-Base, which indicated depression in 5.1% and psychosis in approximately 1.1% of patients receiving vigabatrin.[42]

Noted for mood-stabilizing properties among bipolar patients, gabapentin may positively affect the mood of patients with epilepsy.[43] Small open trials of gabapentin in patients with bipolar disorder refractory to standard therapy have shown the drug to be a successful mood stabilizer.[44-47] Nevertheless, gabapentin was not shown to be more effective than placebo in a small placebo-controlled study evaluating it as an add-on therapy for bipolar disorder.[48]

Lamotrigine showed a significant treatment effect among patients with bipolar I depressed phase in a large double-blind, placebo-controlled trial.[49] Given the efficacy demonstrated by lamotrigine in another double-blind, placebo-controlled study, the drug may also have a role as a monotherapeutic agent for rapid cycling bipolar disease.[50]

Negative neuropsychiatric effects have been reported in epilepsy patients taking topiramate. Slowly titrating topiramate, perhaps increasing the dose by 25 mg every other week, may help minimize neuropsychiatric symptoms.[51] When topiramate was added

to the medication regimen of 44 bipolar patients for whom standard agents had failed, half of the subjects showed marked or moderate improvement in their symptoms.[52] Patients who had been initially manic improved significantly in an open-label, add-on study of topiramate in 56 bipolar patients; both patients and investigators considered the associated appetite suppression and weight loss as favorable.[53] A case report describing three patients with post-traumatic stress disorder noted that topiramate was beneficial.[54]

Although 10% or fewer of the subjects in pre-FDA approval clinical trials of tiagabine experienced nervousness, tremor, and difficulty with concentration, the rate of occurrence was greater than with placebo treatment. Depression was noted with greater frequency than placebo in add-on trials of tiagabine: 3% of 494 treatment-group patients versus fewer than 1% of 275 placebo-group patients.[55] Slow titration, similarly suggested for other AEDs, was recommended to avoid the worsened mood noted in a study converting patients receiving AED polytherapy to tiagabine monotherapy.[56] Given tiagabine's mechanism as a GABA reuptake inhibitor, Meldrum and Chapman[57] suggested a potential role for tiagabine in managing bipolar disorders. Eight patients with acute mania did not benefit from acute treatment with tiagabine,[58] but two patients with bipolar disorder and one with schizoaffective disorder, bipolar type, improved and stabilized when they received adjunctive tiagabine.[59]

The psychoactivity of zonisamide, levetiracetam, and oxcarbazepine has received little attention in the recent medical literature. Nevertheless, a treatment effect was noted among 15 manic bipolar patients who received zonisamide during an open study.[60] As a keto-analogue of carbamazepine, oxcarbazepine may likewise serve to stabilize mood, possibly by enhancing dopaminergic transmission.[61]

Folic acid and depression in epilepsy patients. A potential iatrogenic mechanism for depression in epileptic patients is decreased folic acid concentration. A decrease in serum, red blood cell, and CSF folate levels occurs in 11% to 15% of patients with epilepsy, chiefly caused by AEDs, particularly phenytoin, carbamazepine, and phenobarbitol.[62,63] Folate deficiency and related elevation in total plasma homocysteine has been associated with psychiatric co-morbidity, most often depression, in patients with epilepsy[62] as well as those without epilepsy.[64-66]

Epilepsy surgery. Psychosis and depression may occur in some patients after lobectomy for intractable epilepsy.[67-69] Bladin[67] documented that epilepsy patients can develop behavioral problems in coping with a suddenly seizure-free state. Complete seizure control, however, is a consistent predictor for psychiatric improvement after epilepsy surgery.[69,70] The study by Altschuler et al.[30] of the impact of temporal lobectomy on mood found that nearly three-quarters of patients with intractable complex partial seizures of unilateral temporal origin had their first episode of depression before surgery. Of those, 47% experienced continued relief from depression for an average duration of 9.6 ± 5.2 years after surgery.

Psychosocial factors. Quality of life is often suboptimal for patients with epilepsy, and this may adversely affect mood.[12,71-74] Increased financial stress, life stressors, and poor adjustment to seizures are predictive of increased depression.[41] The lack of control over the illness may be an additional risk factor for depression.[12,75]

Treatments for epilepsy and depression. In nonepileptic patients with bipolar disorder, carbamazepine,[76,77] valproate,[77,78] lamotrigine,[49,50] and gabapentin[45,79] have shown efficacy in the prevention of recurrent manic and depressive episodes and as an antidepressant. However, in patients with unipolar depression, more benefits were reported for carbamazepine and valproate when these agents were used as adjunctive treatments.[80]

Gabapentin has demonstrated psychoactive effects in patients with epilepsy. The results of five double-blind clinical trials showed that 46% of gabapentin-treated patients had improvements in general well-being compared with only 29% for placebo, with the beneficial effect on mood independent of seizure control.[81] A quantitative improvement in mood occurred in patients with complex partial epilepsy with the use of gabapentin as an add-on AED. A significant decrease in the Cornell Dysthymia Rating Scale (CDRS) scores over time was reported in the gabapentin-treated patients relative to controls ($p = 0.04$), again independent of seizure frequency. Although these results do not provide evidence supporting the use of gabapentin as an antidepressant, half of the gabapentin-treated patients who were dysthymic at baseline (score 20 or greater on CDRS) showed an antidepressant effect at 3 months (less than 20 on CDRS).[43] These results suggest that gabapentin, as well as carbamazepine, valproate, and lamotrigine, should be specifically considered for epilepsy patients with depressive symptoms. Conversely, psychiatric decompensation may occur when these mood-stabilizing AEDs are withdrawn during medication changes.

Vagus nerve stimulation. VNS is an approved treatment for patients with medically refractory epilepsy.[82-85] Longer-term efficacy studies of VNS therapy have suggested that seizure reduction is sustained or improved over time.[86-89] In five clinical trials of VNS therapy ($n = 454$), there was a 50% or greater seizure reduction in 36.8%, 43.2%, and 42.7% of patients at 1, 2, and 3 years of VNS therapy, respectively.[90] However, only a few patients achieve full remission of seizures or are able to reduce AEDs significantly.[91]

VNS therapy is now under investigation as a therapy for treatment-resistant depression.[92-94] Its exper-

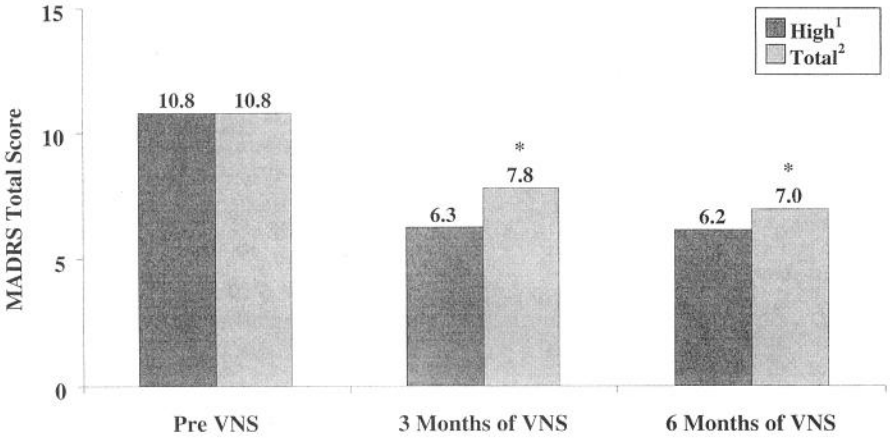

*Figure 1. Improvement in MADRS score at 3 and 6 months of VNS therapy in epilepsy patients. [1]High stimulation (n = 6) (max 1.75 mA; duration 30/300; pulse width 500 us). [2]All patients (n = 11) receiving VNS therapy (total low and high stimulation). *Wilcoxon's test $p < 0.05$ comparing baseline to 3 and 6 months of VNS therapy. Adapted from reference 98, with permission.*

imental application to the treatment of depression evolved as clinical improvements in mood were recognized during studies of patients with epilepsy.[82-86] In addition, the use of AEDs as mood stabilizers and antidepressants in mood disorders provided a basis for exploring the potential antidepressant benefits of VNS therapy.[49,95,96]

Epilepsy patients treated with VNS for 3 months had a significant decrease in mood scale scores across time [CDRS, $p = 0.001$; Hamilton Depression (Ham D), $p = 0.017$; BDI, $p = 0.045$], indicating a reduction in depressive symptoms.[97] An additional study assessed patients after 6 months of VNS therapy and found that mood improvements were sustained (figure 1).[98] Even patients with little or no seizure decrement experience substantial mood improvement.[97,98]

Given the possible antidepressant effects of VNS therapy, an open-label study of 60 patients with treatment-resistant depression was conducted to examine response rates and adverse events and to establish predictors of outcome. The results of this study showed a 31% response rate as measured by the Hamilton Rating Scale for Depression-28 item ($HRSD_{28}$) and an overall 15.3% remission rate after 10 weeks of VNS treatment. Significant improvements in neuropsychological functioning were found in many scales. VNS therapy was well tolerated; none of the 60 patients discontinued because of adverse events. Voice alteration during stimulation was the most common adverse event (55%), followed by coughing (17%) and dyspnea (15%), particularly on exercise. Predictors of poor outcome with VNS treatment were the degree of treatment resistance before study entry (i.e., the greater number of unsuccessful adequate antidepressant treatment trials, the less likely a positive response to VNS treatment) and whether a patient had received electroconvulsive therapy (ECT) or did not respond well to ECT.[93]

Data presented in 2001 from this cohort on the effects of VNS therapy up to 2 years (60 patients at 1 year; 30 patients at 2 years) indicate that the initial response at acute study exit increased at 1 year (31% to 45%; $p = 0.08$) and the remission rate significantly increased (15% to 27%; $p = 0.04$). At 2 years, the initial 30 patients showed a sustained response from 1 year (46% to 54%) for patients who have at least one follow-up assessment beyond 12 months (figure 2).[99] As discussed in the article by George et al.[100] in this supplement, an acute phase, double-blind trial of VNS therapy for depression failed to show a statistically significant difference in response between the VNS group and a control group. However, long-term results continue to show promise and further exploration of VNS therapy for depression is under discussion. VNS holds promise as a treatment for epilepsy patients with depressive symptomatology, and preliminary findings suggest that VNS therapy may be a beneficial therapy for treatment-resistant depression.

Antidepressants. Research on the use of antidepressant medication for treatment of depression in patients with epilepsy has been limited owing to the risk of antidepressant-induced seizures.[12,101] The incidence of seizures when the dose of antidepressants is in the therapeutic range[102] varies from 0.1% to 4% compared with 0.073% to 0.086% in the general population.[103] A meta-analysis of 5,334 and 2,848 depressed patients receiving imipramine and amitriptyline, respectively, reported an incidence[104] of seizures from 0.0% to 0.6%.

Generally speaking, SSRIs, multireceptor antidepressants (nefazodone and venlafaxine), and most tricyclic antidepressants (TCAs) have a low risk for producing or exacerbating seizures when used in the recommended therapeutic range.[105] A study of 43 patients with epilepsy and depression showed citalopram, an SSRI, to be effective as an antidepressant, but without effect on seizure frequency.[106] Seizures worsened in 6% of patients taking sertraline, another SSRI, but were corrected to baseline when AED dosage was adjusted.[107] Clomipramine, however, is a TCA with generally greater seizure risk than others[102] and should be avoided in patients with epilepsy. Maprotiline also has a relatively great seizure risk[108] and should not be used in patients with epilepsy. Bupropion has a seizure risk of 0.35% to

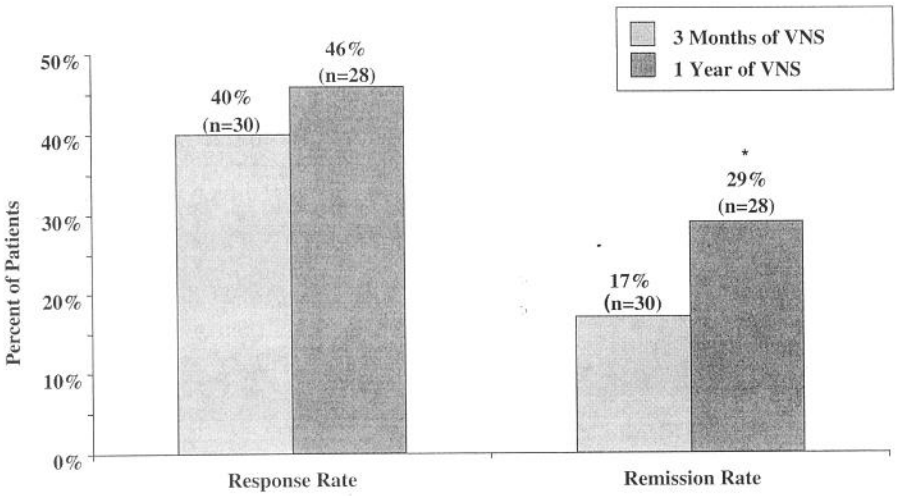

*Figure 2. VNS therapy response and remission rates at 3 months (acute study exit) and 1 year long-term follow-up assessment in patients with unipolar or bipolar depression. *McNemar's exact test p = 0.046 comparing 3 months to 1 year of VNS therapy. From reference 99, with permission.*

0.86%, similar to that of other antidepressants at total daily doses of 450 mg or less, but should not be used at higher doses in epilepsy patients.[109] MAO inhibitors have a low seizure risk, but the other cautions associated with their use require judicious prescribing. Conversely, some investigators have reported an anticonvulsant effect of some antidepressants; however, this effect is not widely accepted by clinicians.[110]

Interactions between antidepressants and AEDs must be considered when patients with epilepsy and depression are treated. Most antidepressants inhibit one or more of the cytochrome P450 isoenzymes in the liver.[111] Many currently prescribed antidepressants (fluoxetine, fluoxamine, nefazodone, paroxetine, and sertraline) produce enzyme inhibition, possibly resulting in toxic levels of the more "classic" anticonvulsants phenytoin, phenobarbital, and carbamazepine. Elevated levels of carbamazepine have been observed during concomitant use with fluoxetine,[112] fluoxamine,[113] and nefazodone.[114] Low doses of sertraline, venlafaxine, or citalopram have little effect on enzyme inhibition and therefore should not produce clinically significant interactions.[12,111,115] Monitoring levels of AEDs may be necessary when antidepressant therapy is initiated.

Some AEDs are potent cytochrome P450 enzyme inducers, including primidone, phenytoin, carbamazepine, and phenobarbital.[116] Most often, clinically significant interactions have occurred when TCAs are introduced, resulting in lower than expected plasma levels and efficacy.[117] For example, barbiturates, phenytoin, or carbamazepine can lower clomipramine or imipramine serum levels. Therefore, a higher TCA dose may be required when these agents are taken together with hepatic-inducing AEDs.

Some adverse effects of antidepressant medication, such as sedation and cognitive impairment, may confound the side effects of various AEDs, symptoms of epilepsy, or depressive illness. Many antidepressants produce sedation,[118,119] causing difficulties for patients who are prescribed AEDs with the same effect (i.e., barbiturates and/or benzodiazepines).[120] Cognitive impairment has been reported with certain antidepressants, confounding the memory and cognitive impairments often observed in both depression and epilepsy.[101,121]

Electroconvulsive therapy. ECT can be safely used in epilepsy patients with severe, refractory, or psychotic depression.[101] An increase in seizure thresholds has been observed during the course of ECT treatment.[122] Consequently, some consider ECT an effective anticonvulsant.[123] Spontaneous seizures, however, may follow ECT.[124] To minimize ECT dose and any related side effects, AEDs should not be given the morning that ECT is administered. Exceptions to this practice are that long-term AEDs should not be reduced in patients with recent generalized tonic–clonic seizures or who are at high risk for status epilepticus.[125]

Conclusion. Interictal depression is common in patients with epilepsy, occurring in 9% to 22% of patients with epilepsy, although the exact prevalence is not known. The etiology of co-morbid depression in patients with epilepsy is multifactorial, including genetic and clinical features of epilepsy (seizure frequency, severity, type of seizure, localization, or lateralization of focus). Iatrogenic mechanisms such as type of AED (phenytoin, topiramate, vigabatrin, tiagabine), secondary effects of AEDs, or polypharmacy are associated with increased risk for depressive symptoms. Psychosocial factors also may play a role, but other biological mechanisms appear to be more influential.

Treatment involves, first and foremost, seizure control with appropriate anticonvulsant therapies. There is evidence that some anticonvulsant therapies, including VNS, valproate, gabapentin, carbamazepine, and lamotrigine, also have antidepressant effects and may prove effective in treating depression in patients with epilepsy. However, antidepressants may be necessary to effectively treat depression in these patients. When an antidepressant is prescribed, the epileptogenic potential, adverse effects, and drug

interactions must be evaluated. Suggested as first-line treatments are SSRIs such as citalopram (due to its lack of drug interactions) and multireceptor-active compounds such as nefazodone or venlafaxine. Bupropion, maprotiline, and clomipramine should be avoided. Electroconvulsive therapy is not contraindicated and may prove effective for epilepsy patients with severe, treatment-resistant, or psychotic depression. It is imperative that depression be recognized and treated in patients with epilepsy. Further prospective studies of new treatment options for depression in this patient population are needed.

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Vagus nerve stimulation therapy

A research update

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Article abstract—Over the past 5 years, and especially within the last year, there has been a rapid expansion of vagus nerve stimulation (VNS)-related preclinical research, as well as clinical studies in indications other than epilepsy. The research advances in understanding VNS are occurring in the midst of a blossoming of other forms of therapeutic brain stimulation, such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS). In general, improved understanding of the neurobiological effects of VNS therapy as a function of the different use parameters (frequency, intensity, pulse width, duration, dose) is beginning to guide clinical use and help determine which diseases, in addition to epilepsy, VNS might treat.

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What is the best approach to determining whether vagus nerve stimulation (VNS) has therapeutic potential in addition to its anticonvulsant properties? In theory, in a perfect world it would be simple to determine which additional neuropsychiatric diseases VNS might treat. As a first step, one would simply outline the full and known neurobiological effects of VNS (both the functional neuroanatomy and the cascade of neurobiological effects that VNS sets into motion). Next, one would list the functional neuroanatomic maps and pathophysiological cascades of the different neuropsychiatric diseases (step 2). In step 3, one would then simply look for overlaps between the VNS effects and anatomy and the pathogenesis and anatomy of neuropsychiatric diseases. One would carry out preclinical and then clinical trials in those diseases with a high probability of a VNS therapeutic effect, using the precise parameters that are known to affect the diseased portion of the brain.

Unfortunately, we are still a long way from realizing this dream. First, despite over two decades of research with functional neuroimaging, there is still inadequate understanding of which areas of the brain are affected in most of the major neuropsychiatric disorders. (Movement disorders, strokes, multiple sclerosis, and Alzheimer's disease are exceptions.) As examples, the dysfunctional neuroanatomy and regional neuropharmacology associated with depression, the anxiety disorders, schizophrenia, autism, obesity, and addictions are still poorly understood. Moreover, despite extensive recent research, scientists do not fully understand which pathways are critical to the VNS signal in the brain. There is inadequate information about the immediate and longer-term translational changes that VNS produces, and how the neurobiological effects of VNS differ as a function of the various use parameters (see the article by Henry, this supplement). Therefore, applying VNS to the different neuropsychiatric disorders, in the absence of much of the needed knowledge about VNS neurobiological effects, still requires informed guesswork rather than strict deterministic applications of known rules. The clinical applications to date have been guided by both observations in the clinic in co-morbid diseases (see, e.g., the article by Harden in this issue about co-morbid depression and epilepsy) and knowledge of vagus nerve function in the light of the disease pathophysiology.

Recent research about VNS neurobiological effects. Elsewhere in this supplement, Henry describes recent advances in understanding VNS mechanisms of action. Below, we highlight some of the recent animal and clinical research findings that help delineate the neurobiological effects of VNS.

In the past, many scientists believed that VNS activated unmyelinated C-fibers and then the reticular activating system. This early theory might be labeled the "cortical desynchronization theory."[1-3] Several researchers were skeptical of this theory, in part because the effective VNS parameters used to treat epilepsy are subthreshold for activating C-fibers.

This past year, Krahl et al.[4] demonstrated that C-fibers are neither necessary nor sufficient for VNS to suppress seizures. In freely moving rats, vagus stimulation of myelinated A- and B-fibers were able to suppress seizures. Zagon and Kemeny[5] also pursued this area using animal studies at a cellular level. These authors found that weak stimuli predominantly affect the myelinated A- and B-fibers and activate cortical pyramidal neurons. Trains of

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vagus stimuli lead to prominent slow hyperpolarization of pyramidal cell neurons, reducing excitability. This work suggests that perhaps VNS affects cortical excitability through mechanisms other than that proposed in the cortical desynchronization hypothesis. Recent work by Dean et al.[6] in epilepsy patients with VNS implanted for 6 to 12 months relates to the preclinical work. These researchers used transcranial magnetic stimulation (TMS) to study the effects of acute VNS on motor threshold (MT) and the cortical silent period (CSP) after a TMS pulse. These are TMS measures of cortical excitability. Most interestingly, motor cortex excitability decreased significantly while VNS was on in patients who had been receiving TMS for over 6 months, compared with the following 30 minutes while VNS was turned off. Obviously, more work is needed to understand which fibers are being stimulated by VNS as a function of the use parameters, and how this correlates with clinical effects.

There has been some recent progress in understanding the brain effects of VNS use parameters [pulse width, intensity, frequency, duty cycle (on, off)], specifically as a function of age. Koo et al.[7] measured threshold current intensity for a single stimulus at various pulse durations and conduction velocity of the vagus nerve in 21 patients (aged 4 to 31 years) during VNS implantation surgery. They found that the vagus nerve is probably not completely myelinated until full adulthood. They demonstrated that, in adults compared with children, the vagus is faster and requires less stimulus current and a shorter pulse width to send a signal to the cortex.

Studies combining functional brain imaging with VNS offer the promise of determining which brain areas are activated by VNS. Fast imaging methods, such as functional MRI (fMRI), can demonstrate the *immediate* effects (2 to 6 seconds) of VNS. Slower imaging methods, such as SPECT and PET, can demonstrate the *longer-term changes* associated with constant VNS over time. Recently, at the Medical University of South Carolina (MUSC) we have succeeded in performing blood oxygenation level-dependent (BOLD) fMRI studies in depressed patients receiving VNS as part of an initial pilot study[8-10] and a more recent and larger double-blind trial. An initial study using the interleaved VNS/fMRI technique showed that VNS immediately activates many anterior limbic regions, including the orbitofrontal cortex, insula, and medial temporal lobe.[11] A follow-up study using the same technique showed that VNS at 5 Hz had a much smaller brain effect than did VNS at 20 Hz.[12] In this small sample there was no statistically significant increase in blood flow with 5 Hz, whereas in the same subjects 20 Hz produced many regions with increased blood flow. Most recently, this same group has used real-time fMRI analysis and repeated within-individual scans to demonstrate the effects of different use parameters on regional brain activity (figure 1). This technique offers the promise of perhaps finding the optimal VNS parameters for a given patient.

Performed before and after several months of VNS therapy, PET scans provide a view of the long-term changes induced by VNS. Figure 2 is an interim analysis in six depressed subjects with VNS. This analysis suggests that VNS over 3 months increases resting metabolism [^{18}F]-fluorine-2-deoxy-D-glucose (FDG PET) in the orbitofrontal cortex, the cingulate gyrus bilaterally, and the left insula.[13] Thus, functional imaging studies are beginning to provide information about the immediate and longer-term changes associated with VNS, and how these are influenced by different VNS parameters and related to clinical response.

Recent clinical studies. Several studies have investigated the clinical effects of VNS in neuropsychiatric diseases other than epilepsy (table 1).

Depression. VNS was initially tested as a potential treatment for depression beginning in July of 1998. This trial was begun on the basis of animal[14] and human brain imaging data showing that acute VNS affects limbic and paralimbic regions known to modulate mood.[15] There was additional support of a potential antidepressant effect of VNS from the positive mood effects of VNS observed in epilepsy patients,[16-18] the knowledge that some anticonvulsants are also antidepressants, and neurochemical studies indicating that VNS has effects on brain monoamines.[19]

An initial pilot open study of VNS in 30 adult outpatients with severe, nonpsychotic, treatment-resistant major depressive episodes reported a 40% response rate after 8 weeks of VNS therapy, using $\geq$50% reduction in baseline Hamilton Depression Rating Scale ($HDRS_{28}$) total score to define response (12/30 responders).[8] This medication-resistant group had been depressed in the current episode for an average of 10 years and had failed to respond on average to more than five research criteria medication trials in that episode. They had averaged 17 clinical trials of medications or electroconvulsive therapy (ECT). There was a 17% complete remission rate (exit $HDRS_{28} < 10$), suggesting the efficacy of this technique in depression. This study was extended for longer-term follow-up, and after 6 months of treatment 17/30 (57%) of the treatment-resistant patients met criteria for response.[10] An additional 30 subjects were added to this open trial, and these subjects had a 21% acute response rate. There was an overall response rate after 8 weeks of therapy (combined in 59 completers) of 30%.[9] An additional analysis found that VNS appeared to be most effective in patients with low to moderate but not extreme antidepressant treatment resistance.[9] That is, those who had failed only two or three research level attempts at antidepression therapy in the index episode were more likely to respond to VNS than were those who had failed more than five research level trials. The device was generally well-tolerated and

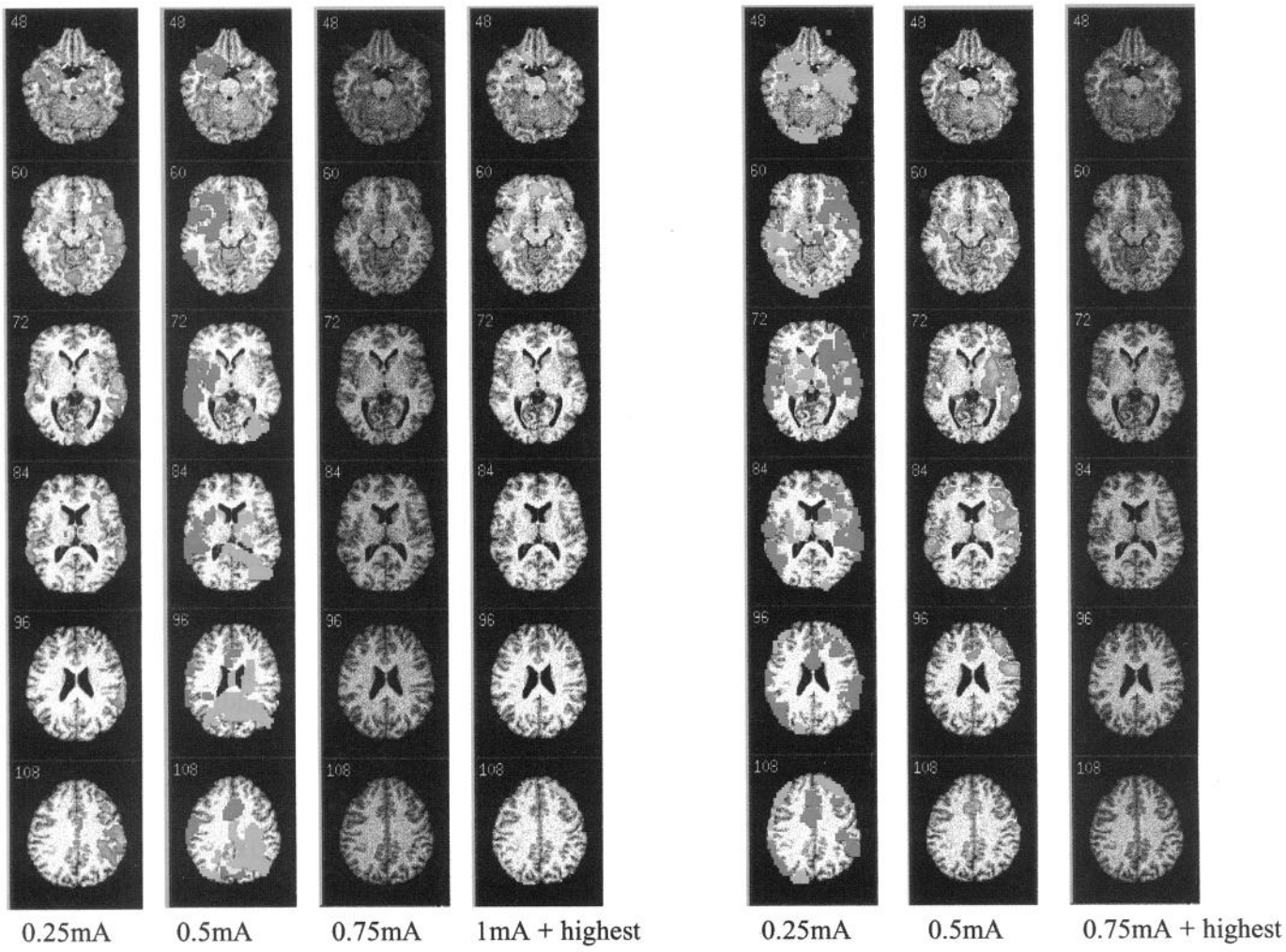

Figure 1. Acute vagus nerve stimulation effects: VNS-induced regional cerebral activity using fMRI in two different depressed subjects, each studied on multiple sessions within the same day, each time with a different VNS intensity. Significant VNS-induced increases are displayed in red, with decreases in blue ($p < 0.05$ for display, merged onto a standard MRI scan in Talairach Space). Note that the acute effects of VNS in these subjects change as a function of frequency. There are acute increases in brain regions known to receive vagus sensory input, i.e., the orbitofrontal cortex, cerebellum, insula, and medial and dorsolateral prefrontal cortex. These same regions are consistently implicated in patients with depression. An important area of research is whether individualized imaging such as this might help determine effective clinical settings. From work in progress at MUSC; figure courtesy of MUSC Center for Advanced Imaging Research (CAIR) and Brain Stimulation Laboratory (BSL).

there was no evidence of adverse cognitive effects.[20] To overcome the limits of these open design studies, a multisite randomized, sham control study has been conducted, with full results pending. It is challenging to conduct a double-blind study with a device and, for this study, all subjects were implanted with a generator. One-half of the subjects had the device turned on 2 weeks after implantation and the other half had the device turned off for the first 12 weeks. Patients and raters did not know whether or not the device was on. A recent press release from Cyberonics has stated that, in this trial, the VNS group failed to show a statistically significant difference in acute response from the sham group. The longer-term response rates appear encouraging. The company and investigators are discussing further studies. Based on the strength of the open pilot data discussed above, VNS has been approved as a treatment for resistant unipolar or bipolar depression in Europe and Canada. It is still considered experimental by the FDA.

Anxiety disorders. Norepinephrine (NE) has long been considered a key neurotransmitter involved in the pathogenesis and regulation of anxiety. A device such as the VNS that directly stimulates the locus ceruleus, which is the primary NE control site, would potentially have important effects on anxiety. The historical importance of this pathway can be

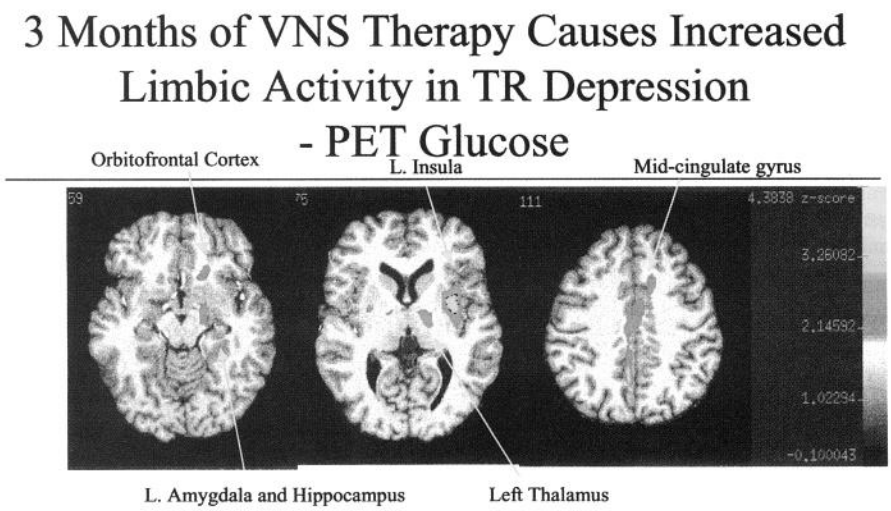

Figure 2. Chronic VNS changes: These PET scans highlight the effects of VNS as a long-term therapy, which is different from the immediate effects of VNS as seen with fMRI. These are preliminary pooled data from St. Louis University in depressed patients involved in the DO2 depression trial.[13] Each person was scanned twice, once at baseline and then again after 3 months of therapy with the device once again turned off 30 minutes before the second scan. The pooled difference images show that, over time, there are increases in many of the same regions at which VNS acts acutely. There were no areas with decreased activity over time. These limbic regions (orbitofrontal, medial prefrontal, insula, and cingulate cortex) are involved in mood and anxiety regulation. Whether these changes are specific to depression in general, or to treatment response in particular, remains to be studied. An important area of future research is to understand how the acute effects of VNS initiate changes over time that then result in clinical effects.

seen in the oldest theory about the brain origins of fear, called the James–Lange theory of emotions.[21] William James[21] and C. Lange[22] proposed the radical argument that all emotion actually resided in the body and that it was the brain's interpretation of this signal through the vagus nerve that caused someone to be anxious. They argued that rather than one becoming anxious and then the heart beating fast and one becoming short of breath, the causal change went the other way. You think you are anxious because your heart beats fast, and then your brain gets this signal (through the vagus) and you experience anxiety. Interestingly, this theory has been hard to disprove, and most modern anxiety researchers think that the ultimate answer lies in feedback loops between the brain and the body. However, all agree that the information flowing through the vagus nerve is probably an important part of anxiety regulation, both afferent and efferent. Obviously, a device that could directly affect that information flow would potentially be a powerful way of altering anxiety. Indeed, strong anti-anxiety effects of VNS were seen in the pilot study in depressed subjects.[8] That is, VNS caused improvements measured on the Hamilton Anxiety Scale that were as clinically and statistically robust as those seen on depression scales. On the basis of this clinical observation of an anti-anxiety effect in the depression study and the theoretical justification given above, a 30-patient pilot open study was recently launched in patients with anxiety disorders (either obsessive–compulsive disorder, panic disorder, or post-traumatic stress disorder).

Obesity. An interesting potential use of VNS concerns the regulation of brain satiety signals. The brain knows that the stomach is empty or full, largely on the basis of information transmitted by

Table 1 *Recent clinical and preclinical VNS studies other than epilepsy*

Disease	Author	Subjects	Key finding
Depression	Rush et al.[8]	30 MDE acute	Open, depression improvement
	Sackeim et al.[9]	60 MDE acute	Depression improvement, smaller, response predictors
	Sackeim et al.[20]	MDE	No adverse cognitive effects of VNS over time
	Marangell et al.[10]	30 MDE f/u	Continued improvement at 1 year
	Rush et al.	240 MDE acute and f/u	Ongoing
	Krahl et al.	Rats	Antidepressant effects in Porsolt Swim Test
Anxiety	Group	8 patients	Ongoing
Obesity	Roslin et al.[24]	10 dogs	Weight reduction in chronic model
	Roslin et al.	Patients	Ongoing
Alzheimer's disease		10 patients	Initial results promising
Migraine			Ongoing

Table 2 *Comparison of VNS and other forms of brain stimulation*

Name	Stimulation Method	Invasiveness	Effectiveness for Depression		US FDA Approved Indications	Anatomy
			Acute	Long-term		
Electroconvulsive therapy (ECT)	Electrical to scalp	5 (repeated general anesthesia)	5	??	Depression, mania, catatonia	Seizure decreases prefrontal/limbic activity
Magnetic seizure therapy (MST)	Magnetic, inducing electrical current	4 (anesthesia, seizure)	??	??	None	Unclear, but theoretically more focal than ECT
Transcranial magnetic stimulation (TMS)	Magnetic, inducing electrical current	1 (awake, alert, no cognitive effects, no seizure)	3	??	None	Focal, causes immediate increase in cortical activity, with deeper subcortical changes
Vagus nerve stimulation (VNS)	Electrical, to vagus nerve in neck	2.5 (one operation, implant of device)	2	2.5	Epilepsy	Increases in OFCx, insula, hypothalamus Different effects on use parameters unknown
Deep brain stimulation (DBS)	Electrical, directly to brain through implanted wire	4 (minor brain surgery, implanted device)	??	??	Tremor, Parkinson's disease	High frequency blocks activity at site of wire, turning it off

the vagus nerve.[23] In theory, one could alter the vagus signal and modify eating behavior. This reasoning led to pilot work in a canine model, in which healthy normal-weight dogs implanted with bilateral subdiaphragmatic VNS devices lost weight over time.[24] These encouraging animal studies led to a recent safety study in morbidly obese humans, which has now been expanded into a larger trial. Interestingly, there has been no documentation of weight loss in the epilepsy and depression trials or, for that manner, in the animal model when VNS was applied through the vagus nerve in the neck. It is believed that higher-intensity stimulation is needed, which is done more easily with subdiaphragmatic VNS.

Pain. Vagus afferents carry pain information to the brain from the gut, and stimulation of the vagus afferents inhibits nociceptive behavior in animal models.[25,26] Therefore, vagus stimulation might, in theory, have a role in the treatment of chronic pain. This area is complex, however, because some studies suggest that low intensities of VNS lead to pronociceptive effects and higher stimulation intensities lead to inhibitory antinociceptive effects.[27,28] Ness et al.[29] confirmed this complexity in humans by studying eight VNS-implanted epilepsy patients and assessing the acute effects of VNS on pain thresholds. VNS, compared with sham (generator turned off), acutely lowered the pain threshold, with the greatest reduction being at an intensity 66% of that used to control their seizures. In contrast to these acute crossover studies and as a preliminary attempt to address the question of whether long-term VNS might treat pain, Kirchner et al.[30] studied 12 VNS epilepsy patients and 12 age- and gender-matched controls at three different time points. The patients were investigated before implantation, 2 to 5 days after starting VNS therapy, and after 8 to 14 weeks of therapy. Compared with controls, the VNS-treated patients had reduced pain response to two different methods of producing pain, squeezing of finger folds and repeated quick painful impacts on the skin. Further study in this area appears to be warranted, with particular attention paid to the differences between acute and chronic changes and the relationship to VNS dose.

Cognition and memory. Beginning with some of the first animal studies, researchers and clinicians have noted that VNS patients and subjects frequently look more alert and focused after several weeks of treatment (personal communication J. Zabara to M. George, January 13, 2002). Moreover, Clark et al.[31] demonstrated that epilepsy patients with specific VNS parameters had improved recognition memory. These observations and others[20,32] raise interest in whether VNS may have a cognitive enhancing effect. An ongoing pilot study is assessing VNS in Alzheimer's disease.

Summary and future directions. The preclinical, imaging, and clinical trials of VNS are exploring its effectiveness in a variety of nonepileptic conditions. These new data about VNS are emerging at a time when there is renewed interest in the entire area of device-based approaches to neuropsychiatric disorders. These therapies range from ECT for the treatment of depression, to TMS as a research and clinical tool, to deep brain stimulation (DBS) as a treatment for Parkinson's disease.[33] Although these devices differ greatly in their method of entry into the brain, as well as their invasiveness, they share in common the use of electrical stimulation of neurons as a route to therapeutic changes by modulating disease-system pathways. They also share the challenge of understanding the effect of use parameter

changes (frequency, intensity, pulse width, total dose) on the brain, and how this relates to the biological effects. Table 2 is an overview of these other related approaches.

In summary, the past 5 years have seen a blossoming of preclinical, human imaging, and clinical trials investigating both the mechanisms of action of VNS and other diseases for which VNS might prove useful. This VNS-related work is being conducted in the context of an explosion of interest in the broader concept of electrically stimulating discrete brain regions to treat neuropsychiatric illnesses. Clearly, the next 5 years will determine which of these other disorders is likely to benefit from VNS.

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