Vagus Nerve Stimulation in the Treatment of Refractory Epilepsy

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Summary: Many patients with epilepsy suffer from persistent seizures despite maximal anti-epileptic drug therapy. Chronic, intermittent vagus nerve stimulation has been proven to be an effective option for many patients suffering from refractory seizures who are not candidates for surgical resection. Although only a small minority of patients will be entirely seizure-free, vagus nerve stimulation, as an ad-

junct to medical therapy, may result in significant improvements in quality of life. Vagus nerve stimulation is generally well-tolerated, as device implantation is associated with a low rate of perioperative complications, and the majority of side effects are stimulation-dependent and thus reversible. **Key Words:** Vagus nerve stimulation, vagal, epilepsy, seizure.

VAGUS NERVE STIMULATION FOR EPILEPSY

Approximately one third of epileptic patients will suffer from refractory seizures despite maximal anti-epileptic drug (AED) therapy, or they will experience unacceptable side effects of their medications. Surgical resection, such as temporal lobectomy for mesial temporal sclerosis, can result in a dramatic reduction in seizure frequency in select patients; however, surgery carries significant risks of permanent neurologic deficits and even death, with reports of operative mortality reaching 3.6% at some centers.¹

Vagus nerve stimulation (VNS) remains the only non-experimental surgical option available for patients who need surgical management but are reluctant to undergo an intracranial procedure. Moreover, as many as 40% of patients are not candidates for surgical resection.² The neurocybernetic prosthesis (NCP) system developed by Cyberonics (Webster, TX) was approved by the United States Food and Drug Administration in 1997 as an adjunct to pharmacotherapy for adults and adolescents (>12 years of age) with refractory partial onset seizures.^{3,4} Here, we review the Cyberonics device, implantation procedure, possible mechanisms of action of VNS-in-

duced seizure suppression, results from efficacy studies, and commonly reported adverse events.

NCP System: Device and Surgical Procedure

The NCP system consists primarily of the NCP generator and lead (FIG. 1). The NCP generator delivers intermittent stimulation with set parameters, including output current, frequency, pulse width, stimulation on-time, and stimulation off-time. Programmed parameters can be adjusted by a clinician to maximize overall benefit using the external NCP programming wand and software. In addition, a hand-held magnet can be used by patients or caregivers to activate VNS in response to an aura or seizure onset.

A number of variations on the operative technique of VNS implantation have been described.³⁻¹⁰ Additional details regarding the surgical procedure have been published previously.¹¹ Due to potentially higher risks of bradycardia and arrhythmias with right VNS, the left vagus nerve has been targeted in the majority of cases.^{12,13} However, a recent report of right-sided VNS in children may call this claim into question.¹⁴ Briefly, typically under general anesthesia, a transverse incision is made at the level of the cricothyroid membrane along the anterior edge of the left sternocleidomastoid muscle. Dissection is performed medial to the sternocleidomastoid muscle, and the inferior cervical vagus nerve is identified in a posterior groove of the carotid sheath. Three centimeters of the nerve are exposed for device implantation. Next, an infraclavicular subcutaneous

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FIG. 1. The neurocybernetic prosthesis generator and lead.

pocket is made for placement of the NCP generator. The VNS lead connector is then tunneled subcutaneously to attach to the NCP generator. Two helical bipolar stimulating electrodes, as well as an anchor tether, are then carefully wrapped around the left vagus nerve, distal to the superior laryngeal nerve and the superior and inferior cervical cardiac branches.¹⁵ Of particular concern is the potential for bradycardia and even complete heart block in as many as 3% of patients during initial electrode placement and testing.^{16–19} The risk of this complication can be minimized by ensuring proper positioning and orientation of the electrode on the nerve and the connector pins in the pulse generator. Intraoperative electrocardiographic monitoring is also recommended during the initial electrode test, and the surgical team should be prepared for advanced cardiac life support if clinically indicated.

The output current is initially set at zero (0 mA) for the first 2 weeks, followed by titration of stimulation to individual patient response. Beginning parameter settings of 30-Hz signal frequency, 500- μ s pulse width, 30 s on-time, and 5 minutes off-time have been found to be effective in double-blind, controlled studies, although

these parameters may vary considerably in practice.^{20,21} Incremental increases in output current of 0.25 to 0.5 mA every 2 to 4 weeks allow for gradual acclimation, and may ultimately increase a patient's tolerance for higher output current if required for optimal seizure control.²²

Rationale and proposed mechanisms of VNS in epilepsy control

Despite its traditional designation as a parasympathetic efferent, the vagus nerve has a mixed composition, with approximately 20% efferent and 80% afferent fibers. The afferent fibers originate in the jugular and nodose ganglia and innervate the nucleus tractus solitarius bilaterally, sending projections to various regions associated with seizure activity.²³ They are comprised largely of small-diameter, unmyelinated C fibers, but also contain smaller numbers of larger-diameter, myelinated A fibers and B fibers.²⁴ It is by stimulation of these afferent fibers that VNS attempts to remotely exert its antiseizure effects on intracranial structures; however, the mechanisms of these effects are largely unknown. Current research is focused on identifying the afferent fiber types that are involved, characterizing altered patterns of cerebral metabolism or

activation with functional neuroimaging or electroencephalography (EEG), and measuring stimulation-responsive neurotransmitters known to modulate seizure activity.

The reduction and/or prevention of pharmacologically-induced seizures by stimulation of C fibers in rats led to the initial conclusion that C fibers figured prominently into the mechanism of VNS.²⁵ However, this finding was called into question by the observation that the clinical efficacy of VNS in humans was maintained at stimulation parameters thought not to exceed the threshold necessary for C fiber activation.²⁶ A subsequent study in rats observed that the VNS-induced seizure suppression remained intact, despite selective destruction of C fibers with capsaicin.²⁷ Further investigation in this area is necessary to determine which afferent fiber types mediate the effects of VNS.

Many thalamic nuclei contain thalamocortical relay neurons with broad projections²⁸ that may modulate propagation of seizure activity.²⁹ The anti-epileptic effects of VNS may be explained in part by changes in trans-synaptic neurotransmission, as reflected by altered thalamic cerebral blood flow. Positron emission tomography has shown that VNS increases bilateral thalamic blood flow, which positively correlates with seizure responsiveness.³⁰ These findings have been supported by single-photon emission computed tomography showing altered cerebral blood flow patterns in the thalamus that also correlate with clinical efficacy.³¹ Thus, VNS-induced modulation of thalamic synaptic activity may contribute to reductions in seizure frequency or severity.

The EEG effects of VNS have been best documented in animal studies, which have demonstrated cortical synchronization or desynchronization, dependent on stimulus frequency and intensity.^{32,33} High-intensity, high-frequency (>70 Hz) VNS produced desynchronization of the cortical EEG in cats, but lower intensity VNS at the same frequency resulted in synchronization. These intensity-specific effects led to the hypothesis that by using careful adjustment of stimulation parameters, VNS may be able to disrupt epileptiform activity by desynchronizing interconnected cortical regions implicated in seizure activity.³⁴ VNS has also been found to produce a variety of EEG changes throughout the sleep-wake cycle in cats, and persistent changes observed during periods of slow-wave sleep in the absence of stimulation suggest that VNS may mediate its long-term effects via induced neuronal plasticity.³⁵ In contrast, VNS has not been shown to produce acute EEG changes in humans. One long-term pilot study observed a decrease in spikes per time interval over 12 months of VNS, but other findings of synchronization or clustering were not consistently observed.³⁶ This EEG finding in the setting of long-term VNS could also potentially correlate with the clinical observation that seizure control appears to improve over

time,^{37–39} but overall the effects of VNS in humans have largely eluded characterization via scalp EEG monitoring.

Neurochemical studies have shown altered concentrations of several amino acids and neurotransmitters, such as ethanolamine in human CSF and brain specimens in response to VNS.^{40,41} This may be an indication of increased amino-acid turnover and increased neuronal activity in regions such as the locus coeruleus.⁴² Moreover, the finding that norepinephrine depletion in the rat locus coeruleus completely abolished the seizure-suppressive effect of VNS further supports the role of this region in seizure propagation.⁴³ The observation of increased *c-fos* expression in response to acute and chronic VNS in rats also supports the role of locus coeruleus activation in the acute phase, along with long-term activation of the NTS, paraventricular nucleus of the hypothalamus, parabrachial nucleus, ventral bed nucleus of the stria terminalis, cingulate cortex, and dorsal raphe nucleus.⁴⁴ A marginal decrease in CSF aspartate with 3 months of VNS is also of interest, given the excitatory properties of aspartate.⁴¹ Indeed, decreased levels of excitatory neurotransmitters may be one factor in the mechanisms underlying improved seizure control.⁴⁵

Clinical outcome of VNS in adults with refractory epilepsy

Considerable clinical evidence exists to support a role for VNS in seizure prevention and amelioration in adults whose seizures have proven refractory to maximal AED therapy (Table 1). Despite these promising results, VNS in its current form is not a curative treatment for epilepsy. Potential additional benefits of VNS include reduction of AED dosage and toxicity, as well as reduced frequency of epilepsy-related hospitalizations; however, it is important to communicate realistic expectations of efficacy prior to implantation. Optimal seizure control can take months to occur, and may require extensive, individualized parameter adjustment over time.

Preliminary results of pilot studies demonstrated significant reduction in the frequency, intensity, and duration of seizures with chronic, intermittent VNS,^{6,7,46–49} which led to subsequent multicenter, double-blinded, randomized controlled trials in adults with medically refractory epilepsy.^{8,21,50,51} These trials demonstrated a mean or median seizure frequency reduction of 24 to 31% over 3 months of follow-up in patients receiving the high VNS treatment paradigm (i.e., VNS at therapeutic stimulatory parameters, such as 30 Hz, 30 s on, 5 min off, and 500-ks pulse width). This improvement was significantly greater than that found in patients in the low or subtherapeutic VNS group (e.g., 1 Hz, 30 s on, 90–180 min off, 1.30-ks pulse width); these patients experienced a mean or median seizure frequency reduction of only 6 to 15%. In fact, one trial noted a 6% median increase in

TABLE 1. *Clinical Outcome of Vagus Nerve Stimulation for Refractory Seizures*

Series	N	Mean Age (y)	Follow-up, (mo)*	Percentage Change in Total Seizure Frequency From Baseline†
Handforth et al. ⁵¹ (1998) ^{‡§}	102	34	3–4	–15.2
Handforth et al. ⁵¹ (1998) [‡]	94	32	3–4	–27.9
Ben-Menachem et al. ²¹ (1994) ^{‡§}	36	35	3.5	–11.3
Ben-Menachem et al. ²¹ (1994) [‡]	31	34	3.5	–30.9
George et al. ²⁰ (1994) [¶]	67	35	16–18	–52
Hornig et al. ⁶³ (1997)	19	12	30	–53.2
Penry and Dean ⁷ (1990)	4	29–39	8.5	–60
Uthman et al. ⁴⁶ (1990)	5	20–59	6	–25.8
Uthman et al. ⁶ (1993)	14	32	3.5–8.75	–46.6
Landy et al. ⁸ (1993) ^{‡§}	5	22–55	3–4.25	12.8
Landy et al. ⁸ (1993) [‡]	4	22–55	3–4.25	–23.1
VNS Study Group ⁵⁰ (1995) ^{‡§}	60	33.5	3	–6.1
VNS Study Group ⁵⁰ (1995) [‡]	54	33.1	3	–24.5
Salinsky et al. ⁵³ (1996) [¶]	100	33.3	10–12	–32
Labar et al. ⁴⁹ (1998)	5	30.2	9	–41
Lundgren et al. ³⁸ (1998)	16	11	2.5–3	–26
Boon et al. ⁶⁰ (1999)	15	29	24	–42.9
Vonck et al. ³⁹ (1999)	25	30	29	–42.9
Hosain et al. ⁶⁶ (2000)	13	16.7	6	–52
Wakai and Kotagal ⁹² (2001)	5	12.3	7.5	–73
Farooqui et al. ⁹³ (2001)	5	11	6.5	–81
Frost et al. ⁶⁷ (2001)	50	13	6	57.9
Scherrmann et al. ⁵⁶ (2001)	95	34.9	16	–30
Majoie et al. ⁹⁴ (2005)	16	11	6	–26.9
Helmers et al. ⁹⁵ (2001)	56	12	6	–44.7
Aldenkamp et al. ⁹⁶ (2002)	19	11.2	24	–20.6
Kawai et al. ⁵⁵ (2002)	13	27	48	–63
Chavel et al. ⁹⁷ (2003)	23	32	24	–40.7
Hui et al. ⁹⁸ (2004)	13	25	18	–40
Holmes et al. ⁹⁹ (2004) [#]	16	36	3–5.25	–43.3
Labar ⁵⁸ (2004)	269	32	12	–58
Spanaki et al. ⁵⁷ (2004)	28	35	60–84	–72
Huf et al. ¹⁰⁰ (2005)	38	36.6	24	–26
Hallböök et al. ⁷³ (2005)	15	11	9	–63
Alexopoulos et al. ⁶⁴ (2006)	16	12.1	36	–74
Rychlicki et al. ¹⁰¹ (2006)	15	11.5	36	–71
Saneto et al. ¹⁰² (2006)	43	8	18	–84
Ardesch et al. ¹⁰³ (2007)	7	17–46	72	–50
De Herdt et al. ¹⁰⁴ (2007)	138	30	44	–51
Kostov et al. ¹⁰⁵ (2007)	12	31	23	–62
Amar et al. ¹⁰⁶ (2008) ^α	921	28	24	–50.5
Amar et al. ¹⁰⁶ (2008) ^β	3822	26	24	–66.7
McGlone et al. ⁶² (2008)	16	35	12	–13.3
Sherman et al. ⁷⁴ (2008)	34	12.3	12	–51.2
Rossignol et al. ¹⁰⁷ (2009)	28	3.5–21	24	–54.8

*We report the longest follow-up period performed in each study when noted; otherwise we report mean or median follow-up times.

†We report the mean (or median) reduction in seizure frequency at the longest follow-up period reported, unless only the overall reduction in mean monthly seizure frequency is reported.

‡Randomized controlled trial.

§Low VNS group: subtherapeutic stimulation parameters.

||High VNS group: therapeutic stimulation parameters.

¶All patients in this trial received high VNS having already exited a randomized controlled trial (Ben-Menachem et al.,²¹ VNS Study Group,⁴⁶ and Handforth et al.⁵¹).

#This study included only patients with pharmacoresistant generalized epilepsy syndromes.

αPrior cranial surgery for epilepsy group.

βNo prior cranial surgery for epilepsy group.

seizure frequency with low VNS.⁸ There were also significant differences in the percentage of patients considered responders ($\geq 50\%$ reduction in seizure frequency),

consisting of 22 to 39% of patients in the high VNS group versus only 13 to 19% of those in the low VNS group.

The use of the hand-held magnet by patients and caregivers to activate the NCP generator directly in response to auras or simple-partial seizures has also reduced the severity of evolving seizures. According to one study, 21% of seizures were reported as aborted with use of the hand-held magnet among patients with therapeutic levels of VNS, compared with only 9% for patients in the low VNS group; a difference that reached statistical significance. In addition, 60% of seizures in the high VNS group were reported as improved when the magnet was used, compared with 40% in the low VNS group, suggesting a moderate but significant benefit over what could be considered equivalent to placebo.²¹ Of note, a post hoc analysis of patients at therapeutic stimulation levels showed that the presence of an aura prior to seizure onset was not required or predictive of efficacy in VNS.⁵¹

After exiting the blinded portion of these trials, all patients were converted to therapeutic levels of VNS and were followed-up for as long as 18 months.^{20,52,53} The percent change in mean seizure frequency relative to baseline was significant for all follow-up periods of VNS, and it was associated with a significant incremental decrease in seizure frequency in the long term. These findings were reinforced by an open-label efficacy trial that enrolled 454 patients from previous randomized, controlled trials, showing sustained median seizure frequency reductions relative to baseline over 3 years of follow-up. Continuation rates of VNS were 97% at 1 year, 85% at 2 years, and 72% at 3 years, demonstrating a high level of overall tolerability and patient satisfaction.⁵⁴

As more long-term, follow-up data on the use of VNS has become available, many centers have observed seemingly cumulative effect on seizure suppression over time.^{39,53–56} In fact, one study noted that six patients considered to be nonresponders after 12 months of VNS therapy began to experience reductions in seizure frequency 4 to 6 years later.⁵⁷ The mechanisms by which this effect might be mediated remain highly speculative, but appear to be unrelated to changes in AED regimens.⁵⁸ Gradual adjustments to stimulation parameters may be responsible for much of these improvements, although the adjustment process is highly individualized and impedes the direct comparison of parameters between studies. In addition, many parameter adjustments are undertaken not only to improve treatment response but also in an effort to improve tolerability, and it is uncertain as to what extent this balance changes over extended periods of stimulation.

Additional benefits of VNS may include reductions in AED requirements and improvements in overall quality of life (QOL) that do not necessarily correlate with seizure control. One prospective assessment of AED regimens over 13 months of VNS demonstrated reductions in

either dosages or number of AEDs in 15 of 21 patients.⁵⁹ These reductions have the potential to diminish both dose-dependent toxicity and costs associated with these medications. Indeed, one cost-benefit analysis has suggested that VNS results in lower net healthcare costs within 2 years of continuous treatment, but this was primarily due in this series to reductions in epilepsy-associated hospitalizations.⁶⁰ QOL is more difficult to assess quantitatively, and the effects of VNS on QOL in adults remain controversial. Significant within-group improvements in subjective measures of seizure relief relative to baseline were observed in one early trial,⁴ and a subsequent 1-year prospective trial reported QOL improvement in 84% of patients.⁶¹ However, these findings have been contradicted by a recent case-control study that found no change in QOL over 12 months of VNS.⁶² These results suggest that there is insufficient evidence at this time to make conclusive statements regarding the effects of VNS on QOL in adult epilepsy.

VNS for refractory seizures in the pediatric population

Experience with VNS in pediatric patients is limited, although studies have shown favorable results in a large proportion (32–53%) of patients treated with adjunctive VNS, ranging from 50 to 90% reductions in seizure frequency at 1 year postoperatively.^{38,63} Long-term, follow-up at 36 months revealed a mean seizure frequency reduction of 74%.⁶⁴ VNS does appear to be a potential option for children under the age of Food and Drug Administration-approved indications. A recent report of VNS in children less than 5 years old demonstrated that 83% of patients had a significant decrease in seizure frequency at 22 months of follow-up.⁶⁵ Atonic seizures were found to best respond to VNS with cessation in two patients. Indeed, younger patients implanted before the age of 12 years appeared to respond better than the older group of pediatric patients.⁶⁴ Notably, children with Lennox–Gastaut syndrome have been shown to respond very favorably to VNS.^{66,67} The efficacy of VNS appears to compare favorably to corpus callosotomy in these patients.⁶⁸ Other studies have demonstrated similar seizure reduction in tuberous sclerosis complex.⁶⁹ VNS has also been successful in refractory nonconvulsive status epilepticus, facilitating prolonged seizure reduction, and partial AED tapering.^{70,71} In contrast to such promising applications, preliminary evidence suggests that VNS is not effective for seizure control or cognitive improvement in patients with comorbid autistic spectrum disorders.⁷² Effects of VNS on QOL in children are also controversial, as two series have found strong associations between improved seizure severity and parental conception of QOL,^{38,73} whereas one did not demonstrate a significant effect.⁷⁴ Nonetheless, the wide range of response rates in children emphasizes the need for a

TABLE 2. Rates of Common Perioperative and Stimulation-Related Adverse Events with VNS for Epilepsy

Series	N	Follow-up Period (mo)	Adverse Events, no. (%)			
			Infection*	Neck Pain	Other Pain	Voice Alteration
Epilepsy						
Handforth et al. ⁵¹ (1998) (LS)	103	3–4	12 (12)		31 (30)	31 (30)
Handforth et al. ⁵¹ (1998) (HS)	95	3–4	11 (12)		27 (28)	63 (66)
VNS Study Group ⁵⁰ (1995) (LS)	60	3		7 (12)	16 (27)	1 (2)
VNS Study Group ⁵⁰ (1995) (HS)	54	3		6 (11)	16 (30)	3 (6)
Labar et al. ⁴⁹ (1998)	5	9	1 (20)			1 (20)
Lundgren et al. ³⁸ (1998)	16	2.5–3		1 (6)		6 (38)
Vonck et al. ³⁹ (1999)	15	29				2 (13)
Hosain et al. ⁶⁶ (2000)	13	6	1 (8)	3 (23)		3 (23)
Wakai and Kotagal ⁹² (2001)	5	7.5		5 (100)	1 (20)	4 (80)
Frost et al. ⁶⁷ (2001)	50	6	2 (4)	5 (10)	5 (10)	22 (44)
Scherrmann et al. ⁵⁶ (2001)	84	16	2 (2)			48 (57)
Majoie et al. ⁹⁴ (2005)	16	6	0 (0)			7 (44)
Helmers et al. ⁹⁵ (2001)	56	6	0 (0)			32 (57)
Hui et al. ⁹⁸ (2004)	13	18		3 (23)		
Holmes et al. ⁹⁹ (2004)	16	3–5.25		3 (19)		14 (88)
Hallböök et al. ⁷³ (2005)	15	9	0 (0)	1 (7)		4 (27)
Alexopoulos et al. ⁶⁴ (2006)	46	36	5 (11)			
Rychlicki et al. ¹⁰¹ (2006)	34	36		4 (12)		15 (44)
Saneto et al. ¹⁰² (2006)	63	18	2 (3)			
Kostov et al. ¹⁰⁵ (2007)	12	23	0 (0)	3 (25)	1 (8)	3 (25)
Rossignol et al. ¹⁰⁷ (2009)	28	24	2 (7)		2 (7)	

Other reported adverse events include ear pain, tooth disorders, insomnia, palpitations, fever, fatigue, hypersalivation, tachycardia, and laryngismus.

HS = high stimulation; LS = low stimulation.

*Infection as the sole perioperative adverse event. All other adverse events are stimulation-related, with incidence as reported at time of follow-up.

better understanding of appropriate indications for VNS in this population.

ADVERSE EVENTS WITH VNS

Perioperative

Generator implantation and electrode placement for epilepsy or depression is generally well tolerated. A large series assessing common complications of VNS reported infections in 7.1% of cases.⁷⁵ The infection rates reported in individual clinical trials of VNS for both epilepsy and depression are summarized in Table 2. The incidence of electrode fracture is low, and device failure was uncommon in recent trials.⁸ Electrode removal is not required for generator or battery replacement, and the electrode is typically left in place in the event of device, removal except in the setting of infection. If required, electrode removal can be accomplished with minimal risk of nerve injury, even several years after implantation and despite the presence of fibrosis.⁷⁶ Voice alteration is most commonly observed in conjunction with stimulation, but may occur postoperatively as a consequence of improper electrode placement, excessive intraoperative manipulation, device malfunction, or patient-inflicted traction injury.⁷⁷ Severe bradycardia and asystole have been reported during intraoper-

ative electrode placement and device testing, but have proven responsive to epinephrine and/or atropine administration, along with brief cardiac compression.⁷⁸ Other uncommon complications in the immediate postoperative period include fluid accumulation in the generator pocket, partial left-sided facial paralysis, and Horner's syndrome.^{51,56,77,79}

Stimulation-related

Rates of common stimulation-induced adverse events are summarized in Table 2. These symptoms are typically experienced transiently during the initial calibration period and are minimized with adjustment of stimulation parameters or diminish in severity with patient acclimation.^{75,77} Of these, voice alteration is most commonly reported during periods of active stimulation, and is likely the result of adduction of the left vocal fold induced by stimulation of the left recurrent laryngeal nerve.^{80,81} This mechanism may also account for the occurrence of some other common adverse events, such as neck or throat pain, dyspnea, and coughing. Vocal fold immobility may occur in some patients during inactive periods due to cumulative damage from chronic, intermittent stimulation, although long-term VNS has not been found to produce histologic evidence of nerve injury.⁸² Preoperative laryngeal electromyography may be useful

TABLE 2. Continued

Adverse Events, no. (%)								
Coughing	Dyspnea	Pharyngitis	Dyspepsia	Dysphagiaa	Nausea	Vomiting	Headache	Paresthesia
				Epilepsy				
44 (43)	11 (11)	26 (25)	13 (13)		21 (20)	14 (14)	24 (23)	26 (25)
43 (45)	24 (25)	33 (35)	17 (18)		14 (15)	17 (18)	23 (24)	17 (18)
5 (8)	1 (2)						5 (8)	2 (3)
4 (7)	3 (6)						1 (2)	3 (6)
2 (40)	1 (20)							
	2 (13)							
3 (20)				1 (7)				
3 (23)								
2 (40)								
15 (30)	2 (4)		2 (4)	1 (2)	2 (4)	1 (2)		4 (8)
3 (4)	2 (2)			3 (4)				
4 (25)				1 (6)				2 (13)
21 (38)				1 (2)				
3 (23)								
1 (6)				2 (13)				
	1 (7)							1 (7)
	1 (2)							
	3 (25)							1 (8)
	1 (4)			1 (4)				

in identifying patients at risk for long-term vocal fold or phonation abnormalities.⁸³ Patients with comorbid obstructive sleep apnea may be at increased risk for apneic episodes during periods of VNS activation while asleep, and preoperative polysomnography in high-risk patients has been advocated.^{84–86} VNS may cause a mild increase in gastric acid output, but does not affect ulcer formation or vital signs.^{51,77} Targeted studies have reported no or minimal effects on cardiovascular parameters during periods of stimulation in patients without underlying heart disease.^{87,88} Outpatient 24-hour Holter monitoring has also failed to demonstrate any clinically significant adverse effects on cardiac rhythm within recommended stimulation parameters.^{54,89} In one series, long-term follow-up of patients with a history of bradycardia during intraoperative lead testing suggests that postoperative reactivation and chronic stimulation are not associated with recurrence.¹⁷ Despite these findings, a late-onset, stimulation-related bradyarrhythmia has been described presenting as syncopal episodes 2 years after device implantation in a patient with a normal intraoperative lead test.⁹⁰ As a result, it is recommended that patients with a history of intraoperative bradyarrhythmia or asystole undergo continuous electrocardiographic monitoring during postoperative device initialization, and further evaluation with electrocardiographic

and/or Holter monitoring is recommended in all patients with symptoms suggestive of a possible arrhythmia. Although sudden, unexplained deaths have occurred in patients undergoing VNS for epilepsy at higher rates than in the general population, rates of sudden, unexplained death and overall mortality have been found to compare favorably to those of other cohorts undergoing treatment for refractory epilepsy.^{55,57,91}

CONCLUSION

Chronic, intermittent VNS as an adjunct to AED, has been well documented as a treatment option for patients with refractory seizures that provides a significant reduction in seizure frequency and severity, as well as an improvement in QOL. VNS is associated with a low rate of perioperative complications, and the majority of side effects are stimulation-dependent and thus reversible. Despite these relative benefits, VNS should not be considered a substitute for intracranial surgery in patients considered good surgical candidates, because in this subgroup the efficacy does not approach that of surgical resection. More than a decade of Food and Drug Administration approval has allowed for the emergence of a well-defined role for VNS in seizure prevention and

amelioration. Further study is necessary to determine the role of VNS for other potential indications.

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