Vagus Nerve Stimulation for Epilepsy and Depression

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Summary: Many patients with epilepsy suffer from persistent seizures despite maximal antiepileptic drug (AED) therapy. Chronic, intermittent vagus nerve stimulation (VNS) has proven to be a safe, effective option for patients suffering from refractory seizures who are not candidates for surgical resection. Although only a small minority of patients will be entirely seizure-free, VNS as an adjunct to medical therapy does appear to provide a significant amount of improvement in quality of life. Reports of antidepressant effects independent of seizure control, along with the use of multiple AEDs in the treatment of depression, has led to the investigation of VNS as a potential adjunctive treatment for major depressive disorder. Both the number of severely depressed patients refractory to available pharmacologic options and the need for repeated treatments and significant side effects associated with electroconvulsive therapy have heightened the interest in VNS for this patient population. Pilot studies of VNS for depression have shown impressive response rates; however, the effect appears to be gradual in onset, as demonstrated by the lack of a favorable response in a short-term, randomized controlled study. Investigation is thus needed to establish the potential role of VNS as an adjunctive treatment for severe depression. **Key Words:** Vagus nerve stimulation, vagal, epilepsy, seizure, depression.

VAGUS NERVE STIMULATION FOR EPILEPSY

Approximately one third of patients suffering from epilepsy will have persistent seizures despite maximal antiepileptic drug (AED) therapy or will experience unacceptable side effects. Although surgical resection can result in 90% reduction in seizure frequency in select patients with classic mesial temporal sclerosis, complete control rates are lower in most patients who undergo epilepsy surgery. In addition, surgical resection for epilepsy can be associated with morbidity in the form of permanent neurologic deficits and even death in ≤4% of cases.[1]

Vagus nerve stimulation (VNS) remains the only nonexperimental option currently available for patients who desire surgical treatment but who are not candidates for, or are unwilling to undergo, an intracranial procedure. Up to 40% of patients are not candidates for surgical resection.[2] The neurocybernetic prosthesis (NCP) system developed by Cyberonics (Webster, TX) was approved by the U.S. Food and Drug Administration (FDA) in 1997 as an adjunct to pharmacotherapy for adults and adolescents over the age of 12 years with refractory partial onset seizures.[3,4] Here, we review the Cyberonics device, implantation procedure, possible mechanisms of action of VNS-induced seizure suppression and mood alteration, 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 parameters that include 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 NCP 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, superimposing a pulse of stimulation on the already programmed intermittent pulses.

A number of variations on the operative technique of VNS implantation have been described.[3–10] Implantation of the vagal nerve stimulator is typically performed under general anesthesia, to minimize risk of an intraoperative seizure, although regional cervical blocks have also

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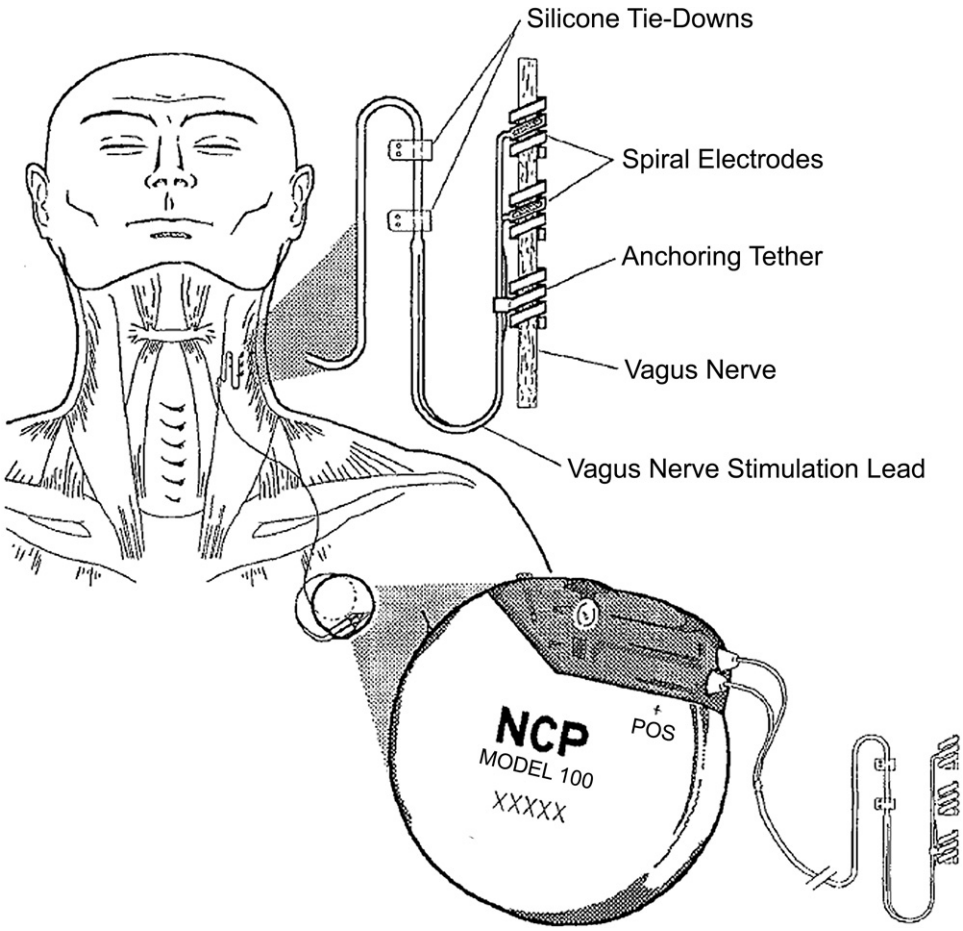

FIG. 1. The neurocybernetic prosthesis generator and lead. Adapted from Ben-Menachem et al.,[16] with permission from Blackwell Publishing.

been used with success.[7] Patients are positioned supine, with the head rotated slightly to the right. A transverse incision is made over the anterior region of the left sternocleidomastoid muscle (SCM) at approximately the level of the cricothyroid membrane (C5/C6). A self-retaining retractor is placed vertically, to open the platysma parallel to its muscle fibers, and dissection is performed medial to the SCM, to obtain a 2.5- to 3.5-cm horizontal exposure of the carotid sheath. The inferior cervical vagus nerve is usually identified in a posterior groove of the carotid sheath between the carotid artery and jugular vein. Three centimeters of the nerve are exposed, using vessel loops. The left vagus nerve has been targeted in the majority of cases, due to potentially higher risks of bradycardia and arrhythmias with right VNS[11]; however, a recent report of right-sided VNS in children may call this claim into question.[12]

Next, an incision is made 8 cm inferior to the midpoint of the clavicle, and a subcutaneous pocket is made for placement of the NCP generator. Alternatively, a more lateral incision in or near the axilla may be used to create a subpectoral pocket that minimizes the cosmetic impact of the generator implant. A tunneling tool is used to create a subcutaneous path from this infraclavicular pocket to the neck region, to attach the connector end of the VNS lead 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 cervical cardiac branches.[13] Before it is placed in the infraclavicular pocket and the incisions are closed, the generator is interrogated electronically to ensure proper function. Bradycardia, and even complete heart block, can occur during testing in 0.1% of patients.[14]

The output current is usually set at zero (0 mA) for the first 2 weeks postoperatively, followed by titration of the stimulation to individual patient response and tolerance. Beginning parameter settings of 30-Hz signal frequency, 500-μs pulse width, 30 s on-time, and 5 minutes off-time have been found to be effective in double-blind, controlled studies, though these parameters may vary considerably in practice.[15,16] Postoperatively, neck and chest radiographs may be obtained to confirm placement of the NCP generator and electrode. Patients are frequently admitted overnight after implantation of the stimulator, although the operation can be performed on an outpatient basis.

Rationale and mechanism of action of VNS in epilepsy control: evidence from animal studies

Although the precise mechanisms of action of VNS are unclear, initial evidence from neuroradiology, neurochemistry, neuroanatomy, and neurophysiology has shed some light on how its clinical effects are mediated. Rapid changes in regional cerebral blood flow (CBF) are thought to reflect transsynaptic neurotransmission.[17] Many thalamic nuclei contain thalamocortical relay neurons with broad projections[18] that synchronize cortical electrical rhythms[19] and thus play a part in terminating or halting propagation of seizure activity. Positron emission tomography (PET) has shown that blood flow in the thalamus increases bilaterally in response to left VNS, and positive correlation between this CBF pattern with seizure responsiveness[20] suggests that therapeutic VNS may decrease seizure frequency or severity by increasing thalamic synaptic activity.

Neurochemical studies have shown altered concentrations of several amino acids and neurotransmitters in human CSF in response to VNS. Significant increases in ethanolamine have been found in patients receiving VNS,[21] as well as in brain specimens of patients with epilepsy.[22] This may be an indication of increased amino-acid turnover and is consistent with elevated *fos* expression, representing increased neuronal activity in regions such as the locus coeruleus.[23] 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.[24] A marginal decrease in CSF aspartate with 3 months of VNS is of interest, given the excitatory properties of aspartate.[21] Indeed, decreased excitation may be one factor in the mechanisms underlying improved seizure control.[25]

The vagus nerve is composed largely of small-diameter, unmyelinated C fibers known to innervate the nucleus tractus solitarius (NTS) bilaterally, sending projections to various regions associated with seizure activity.[17] Stimulation of vagal C fibers in male rats at 10–20 Hz and 0.5–1 ms has been shown to reduce or even prevent seizures induced by intraperitoneal pentylenetetrazol, 3-mercaptopropionic acid, and electroshock.[26] The effectiveness of this treatment was correlated with the fraction of C fibers stimulated. Evidence against these findings includes a lack of significant effect on autonomic function, such as heart rate and blood pressure, which would be expected if C fibers were stimulated.[27] A more recent study observed no effect on VNS-induced seizure suppression in response to selective destruction of C fibers with capsaicin.[28] Certainly, further investigation in this area is necessary to better assess the role of C fibers in VNS.

VNS-induced EEG changes have been well documented.[29] Animal studies have demonstrated electroencephalographic synchronization or desynchronization with VNS, depending on stimulus frequency and intensity.[30] 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, with careful adjustment of stimulatory parameters, VNS may be able to disrupt epileptiform activity by desynchronizing interconnected cortical regions implicated in seizure activity.[31]

Although human studies have not shown significant acute EEG changes with VNS, long-term effects of VNS include clustering and synchronization of epileptiform spike–spike and wave (SSW) activity with progressive prolongation of spike-free intervals. Paroxysms of SSW activity also decrease in duration and frequency with VNS, particularly in patients with prominent epileptiform activity.[32] Thus, VNS may induce an initial synchronization of epileptiform activity followed by a period of desynchronization that increases in duration with time. These changes were more apparent throughout the 1-year follow-up period. Alternatively, intermittent VNS may induce alternating synchronization and desynchronization with the latter being the dominant change. This electroencephalographic finding correlates with the clinical observation that VNS can take months to achieve optimum seizure control.[33–35] The observation of more significant EEG changes in patients with more active and frequent epileptiform activity suggests that these patients may benefit most from VNS.[35]

Clinical outcome of VNS in adults with refractory epilepsy

VNS in various animal models has effectively blocked interictal spikes on EEG, terminated seizures, reduced seizure frequency, and even provided for a period of an anticonvulsant effect despite discontinuation of VNS.[29,36–38] Encouraging results from these studies have led to the development of a programmable pulse generator and electrode lead for VNS in humans with refractory partial seizures. Reported clinical outcomes from studies of VNS for refractory seizures are summarized in Table 1.

Preliminary results of pilot studies demonstrated significant reduction in the frequency, intensity, and duration of seizures with chronic, intermittent VNS.[6,7,39–42] One pilot study indicated that the frequency of seizures of all types were reduced, although the sample was too small to allow any conclusions about which seizure types were most sensitive to VNS.[42] VNS may also decrease the annual number of hospital admissions required per year, as well as epilepsy-related direct medical costs.[43]

These open-label pilot studies led to the onset of multicenter, double-blind, randomized control trials for VNS in medically refractory epilepsy.[8,16,44,45] Results from these trials revealed a mean or median seizure frequency

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

Series	*N*	Mean Age, yr	Follow-up, mo*	Percentage Change in Total Seizure Frequency From Baseline†
Handforth et al.[45] (1998)‡§	102	34	3–4	−15.2
Handforth et al.[45] (1998)‡‖	94	32	3–4	−27.9
Ben-Menachem et al.[16] (1994)‡§	36	35	3.5	−11.3
Ben-Menachem et al.[16] (1994)‡‖	31	34	3.5	−30.9
George et al.[15] (1994)¶	67	35	16–18	−52
Hornig et al.[56] (1997)	19	12	30	−53.2
Penry and Dean[7] (1990)	4	29–39	8.5	−60
Uthman et al.[39] (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[44] (1995)‡§	60	33.5	3	−6.1
VNS Study Group[44] (1995)‡‖	54	33.1	3	−24.5
Salinsky et al.[49] (1996)¶	100	33.3	10–12	−32
Labar et al.[42] (1998)	5	30.2	9	−41
Lundgren et al.[34] (1998)	16	11	2.5–3	−26
Boon et al.[43] (1999)	15	29	24	−42.9
Vonck et al.[35] (1999)	25	30	29	−42.9
Hosain et al.[60] (2000)	13	16.7	6	−52
Wakai and Kotagal[99] (2001)	5	12.3	7.5	−73
Farooqui et al.[100] (2001)	5	11	6.5	−81
Frost et al.[61] (2001)	50	13	6	57.9
Scherrmann et al.[52] (2001)	95	34.9	16	−30
Majoie et al.[101] (2005)	16	11	6	−26.9
Helmers et al.[102] (2001)	56	12	6	−44.7
Kawai et al.[51] (2002)	13	27	48	−63
Chavel et al.[103] (2003)	23	32	24	−40.7
Hui et al.[104] (2004)	13	25	18	−40
Holmes et al.[105] (2004)#	16	36	3–5.25	−43.3
Labar[54] (2004)	269	32	12	−58
Spanaki et al.[53] (2004)	28	35	60–84	−72
Huf et al.[106] (2005)	38	36.6	24	−26
Hallböök et al.[58] (2005)	15	11	9	−63
Alexopoulos et al.[57] (2006)	16	12.1	36	−74
Rychlicki et al.[107] (2006)	15	11.5	36	−71
Saneto et al.[108] (2006)	43	8	18	−84
De Herdt et al.[109] (2007)	138	30	44	−51
Kostov et al.[110] (2007)	12	31	23	−62

*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.,[16] VNS Study Group,[44] and Handforth et al.[45]). #This study included only patients with pharmacoresistant generalized epilepsy syndromes.

reduction of 24–31% 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, 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 6–15%. In fact, one trial noted a 6% median increase in seizure frequency with low VNS.[8] These studies reported ≥50% reduction in seizure frequency in 22–39% of patients in the high VNS group, whereas this was true for only 13–19% of those in the low VNS group. One trial demonstrated significant within-group improvement relative to baseline in subjective measures of seizure relief.[4]

In these trials, patients or their caregivers had access to a hand-held magnet to activate the NCP Generator directly in response to auras or simple-partial seizures. According to one study, 21% of the 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. Addition-

ally, 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.[16] It is interesting that the low VNS group reported a favorable response to the use of the magnet, because in fact (unbeknownst to the patients) no additional stimulation was provided.

In contrast to these findings, a later randomized trial demonstrated no difference in the reduction of seizure frequency in patients without auras, relative to patients with auras.[45] Although no significant changes in AED levels have been noted,[16,45] one study, which prospectively assessed drug reduction in 21 patients undergoing VNS compared with a case-matched control group at 13-month follow-up, demonstrated significant AED reduction in a large proportion of patients.[46] Notably, VNS does appear to be associated with an improvement in quality of life (QOL). Indeed, a 1-year prospective trial of VNS for intractable epilepsy showed significant improvement in mean overall QOL, and subjective improvement was found in 84% of the 26 patients studied.[47]

After exiting the blinded portion of these trials, patients were followed for up to 18 months, all of whom received therapeutic levels of VNS, given the apparent therapeutic benefit.[15,48,49] Mean seizure frequency percent change was significant for all follow-up periods of VNS, relative to baseline. There did appear to be a significant incremental decrease in seizure frequency in the long term.

VNS was well tolerated. For example, at 18-month follow-up, all but 6 patients were continuing therapy; of the six lost to follow-up, one was an unrelated death and the remaining five patients elected to discontinue therapy due to an unsatisfactory result.[15] These findings were reinforced by an open-label, long-term efficacy trial that enrolled 454 patients from these previous randomized clinical control trials.[50] Continuation rates of VNS were 97% at 1 year, 85% at 2 years, and 72% at 3 years, demonstrating overall tolerability and patient satisfaction. Indeed, median seizure frequency reductions relative to baseline were sustained at 3 years of follow-up.

Even though long-term results of VNS on seizure suppression appear to demonstrate cumulative effects over time, consistent with previous reports,[35,49–53] the mechanism by which better seizure control is obtained remains largely unknown. In fact, one study noted a delayed effect of VNS in six patients who did not respond to 12 months of VNS therapy but who experienced reductions in seizure frequency 4–6 years later.[53] These delayed improvements appeared to be unrelated to changes in AED regimens.[54] Adjustments in device settings may play a large role; however, only a trend of an association between these changes and seizure frequency was found in one study.[51]

The most commonly modified stimulatory parameters are output current and off-time.[55] Preliminary evidence exhibited less change in seizure frequency (median reduction, 38%) with a high output current (≥2.25 mA) than with low (0.25–1.00 mA; 64% reduction) and medium (1.25–2.0 mA; 61% reduction) output currents.[54] No significant difference in seizure reduction was found between standard off-times (≥3.0 min; median reduction, 62%) and rapid off-times (≤1.8 min; 50% reduction). Further study in a randomized, controlled fashion is necessary to allow conclusions about the most effective stimulatory parameters for epilepsy control.

VNS for refractory seizures in the pediatric population

Experience with VNS in pediatric patients is limited, although promising data mirror results in the adult population. Studies have shown favorable results in a large proportion (32–53%) of pediatric patients treated with adjunctive VNS, ranging from 50–90% reductions in seizure frequency at ~1 year postoperatively.[34,56] Long-term follow-up at 36 months revealed a mean seizure frequency reduction of 74%.[57] Strong associations between improved seizure severity and QOL have been made, as has been seen in the adult population.[34,58] In fact, ≤80% of patients had an improvement in the parental conception of the child's QOL.

VNS does appear to be a potential option for children under the age of FDA-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.[59] 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.[57] Notably, five of six children with Lennox–Gastaut syndrome had a 90% reduction of seizures at 30 months of follow-up. Other studies have demonstrated similar favorable responses of seizures associated with Lennox–Gastaut to VNS.[60,61] Nonetheless, the wide range of response rates in the pediatric population demands a better understanding of which patients will respond best to VNS.

VAGUS NERVE STIMULATION FOR TREATMENT-RESISTANT DEPRESSION

Major depressive disorder (MDD) is a chronic, debilitating psychiatric illness projected to be the second leading cause of disability worldwide by 2020.[62] The prevalence of MDD is estimated to be as high as 10%, with a lifetime risk of up to 17%.[63,64] Thus, ~30 million American adults may suffer from MDD, with one third classified as severely depressed according to DSM-IV-TR.[65,66] Severe depression has been associated with high rates of comorbidities and mortality, decreased work productivity, and decreased QOL.[67] Direct and indirect costs in the United States are estimated to be as high as 80

billion dollars per year.[68] Response rates to conservative management with FDA-approved antidepressants range from 45–55%, and remission rates can be as low as 30%. Although polytherapy may benefit some individuals, electroconvulsive therapy (ECT) has been associated with the highest remission rates. Unfortunately, ECT is very costly, has well-documented side effects (including significant short-term memory deficits), often requires hospitalization and repeated treatments to maintain efficacy, and is associated with substantial social stigma.[69] Furthermore, remission rates associated with ECT in the community setting are significantly less than what has been reported in clinical trials.[70] Given the pervasiveness of severe depression and the lack of efficacious, safe, and socially acceptable therapeutic strategies, alternative approaches are being investigated.

Left VNS for refractory epilepsy has become a well-established, safe, and effective treatment method as an adjunct to medical therapy. Although the patient sample was small and findings were of marginal significance, Elger et al.[71] in 2000 demonstrated an antidepressant effect of VNS in patients included in the randomized control trial assessing VNS for refractory seizures.[16] These mood improvements were sustained at 6 months of follow-up and were shown to be independent of antiseizure effects. Furthermore, surrogate markers of mood alteration such as improved psychosocial function, attention, temperament and the ability to cooperate have been reported in association with VNS.[72]

The NTS is known to send projections to regions implicated in mood.[17] Moreover, AEDs such as carbamazepine, valproate and gabapentin, have been shown to play a major role in the pharmacologic treatment of mood disorders.[73,74] Findings such as these have paved the way for FDA approval in 2005 of adjunctive VNS in the United States for patients who are at least 18 years of age with treatment-resistant major depression (TRMD) (unipolar and bipolar), which is defined as a failure to respond to $\geq$4 antidepressant trials.[75] Those with bipolar disorder should either be resistant, intolerant, or have a medical contraindication to lithium.[76]

Rationale and mechanism of action of VNS in depression: evidence from animal studies

Studies of functional MRI (fMRI) in depressed patients have reported bilateral VNS-induced increases in blood oxygenation level-dependent (BOLD) activity in various regions implicated in mood disorders and regulated by the vagus nerve.[77,78] These fMRI studies, however, reported no BOLD changes in the thalamus. Furthermore, regional CBF studies using PET in TRMD did not find thalamic changes,[79] although these have been noted in patients with epilepsy.[20]

This apparent contradiction may be a function of distinct disease processes. Both fMRI studies[77,78] and PET studies[79,80] have demonstrated enhanced blood flow and activity in orbitofrontal cortex, as well as other frontal regions. Decreased blood flow was found in the subgenual cingulate cortex, hippocampus, insula, amygdala, and temporal and parietal regions in response to VNS. These imaging findings are consistent with a depression model hypothesizing an imbalance of limbic–frontal circuitry, with frontal hypometabolism and limbic hypermetabolism.[81] A similar mechanism of action of blood flow normalization has been hypothesized for pharmacologic antidepressant treatments. Indeed, intermittent VNS in the rat produced antidepressant effects that equaled two standard antidepressant treatments.[82]

Other findings that suggest a role for VNS therapy of depression include effects on brain regions associated with the norepinephrine[24] and serotonin neural systems.[21] The locus coeruleus and dorsal raphe nucleus are the major sources of norepinephrine and serotonin in the human brain, respectively. Projections of the NTS to the locus coeruleus and raphe nucleus are potentially relevant to VNS mechanisms because of the antidepressant effects of norepinephrine and serotonin. Significant increases in neuronal firing rates in the rat dorsal raphe nucleus and locus coeruleus have been demonstrated after long-term treatment with VNS.[83] Depletion of norepinephrine by a 6-hydroxydopamine infusion into the locus coeruleus completely abolished the seizure-suppressive effect of VNS.[24] Furthermore, the serotonin metabolite, 5-HIAA, increased by 33% in the CSF of patients undergoing 3 months of VNS.[21] Thus, the effects of VNS are at least in part mediated by neurotransmitters largely implicated in the pathophysiology of depression.

Clinical outcome of VNS for treatment-resistant major depression

The clinical response rates after VNS for depression in six human trials are summarized in Table 2. The first report of VNS in adult outpatients was an open-label, nonrandomized trial of 30 patients who met the criteria for MDD or bipolar I or II disorder and were currently suffering from a major depressive episode. The results of this study suggested efficacy of VNS for treatment-resistant depression, with an overall 40% response rate according to the 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) and a 17% remission rate.[84]

VNS parameters were set at 0.25mA, 500-ms pulse width, and 20- to 30-Hz frequency for 30 s on and 5 min off in the majority of patients. Symptomatic responses were accompanied by substantial improvements in overall function, according to the Medical Outcomes Study 36-Item Short Form (MOS SF-36), a measure of mental, physical, social, emotional, and general health, as well as the Global Assessment of Function (GAF). Three of the 12 responders (25%) exited the study with emotional levels equal to population norms. Other findings of this

TABLE 2. *Clinical Response Rates After VNS for Depression in Six Human Trials*

Series	Study Type	*N*	Age, yr, mean ± SD	Follow-up Period, mo	Outcome Measure	Response Rate, %*
Rush et al.[84] (2000)	Open pilot	30	47.5 ± 7.5	0.25	$HRSD_{28}$	40
Sackeim et al.[76] (2001)	Open pilot	59	46.8 ± 8.7	0.25	$HRSD_{28}$	30.5[†]
Marangell et al.[86] (2002)	Open pilot	28	N/A	12	$HRSD_{28}$	46[‡]
Nahas et al.[85] (2005)	Open pilot	59	46.8 ± 8.7	24	$HRSD_{28}$	42[§]
Rush et al.[89] (2005)	Randomized, controlled	112	47.0 ± 9.0	0.25	$HRSD_{24}$	15.2[‖]
Rush et al.[90] (2005)	Open follow-up	205	46.3 ± 8.9	12	$HRSD_{24}$	27[¶]

HRSD = Hamilton Rating Scale for Depression (24-item or 28-item); N/A = not available.
*Defined as a decrease of ≥50% in primary outcome measure. [†]*N* consists of original cohort of 30 from Rush et al.,[84] plus additional cohort of 29. [‡]*N* consists of original cohort of 30 from Rush et al.,[84] minus patients lost to follow-up at 12 months. [§]*N* consists of original cohort of 30 from Rush et al.,[84] plus additional cohort of 29 from Sackeim et al.[76] [‖]$p = 0.251$, for comparison with sham treatment group (10.0%, $n = 110$). [¶]*N* consists of active treatment group from initial 12-week trial, plus previous sham treatment group subsequently exposed to 9 months of active VNS.

study were suggestive of the antidepressant activity of VNS, such as the onset of hypomania in one patient and the fact that two patients responded to VNS without taking pharmacologic antidepressants; however, the small sample size and lack of control group preclude any conclusions about VNS efficacy in TRMD.

Sackeim et al.[76] demonstrated that clinical response rates are typically gradual. Nearly 70% of the patients included in this study did not demonstrate any response to VNS for 6 weeks after the onset of stimulation similar to the effect of VNS on seizure activity. Other studies have shown sustained effects of VNS on levels of depression for 2 years after surgery.[85] Ninety-one percent of responders at 3 months postoperatively remained responders at 12 months.[86] In addition, three nonresponders at 3-month follow-up became responders over the course of the next 9 months.

Another long-term study reported that 39% of the initial nonresponders actually showed substantial benefit at 24-month follow-up.[85] Additional evidence supporting adjunctive VNS for TRMD comes from a recent study comparing the antidepressant benefit of VNS plus conservative management to conservative management alone; VNS plus conservative treatment resulted in a greater response rate per month across 12 months than did conservative management alone.[87] These findings are promising, given that long-term studies of ECT have demonstrated significant relapse rates as high as 50% at 1-year follow-up.[88]

The improvements in mood observed during open-label studies of VNS for epilepsy were noted to accumulate gradually throughout the treatment period. Thus, the unremarkable results of initial randomized trials of adjunctive VNS *versus* sham for TRMD at 10 weeks were attributed in part to the limited duration of treatment. Note, however, that the 30-item Inventory of Depressive Symptomatology Self-Report (IDS-SR30) used to measure self-reported depressive symptoms did demonstrate a significant response to VNS. Open, combined follow-up of patients from both treatment groups of the initial randomized trial after both were assigned to 1 year of active VNS revealed favorable response and remission rates consistent with previous pilot studies.[89,90]

Long-term follow-up of VNS has revealed that most individuals largely maintained or even gained further clinical benefit in overall function, according to the MOS SF-36.[86] Only 9 of 59 patients in one long-term study fell to less than the 40% benchmark from follow-up at 12-months to that at 24-months; however, the same study demonstrated improvement in status in 8 patients from nonresponders to responders during the same time period.[85] Responders to VNS (31%) in one study exhibited remarkable improvement in most aspects of QOL; however, significant QOL improvements were also seen in patients considered nonresponders.[76]

These results raise the issue of placebo effects potentially associated with VNS implantation, and suggest that additional randomized trials with longer treatment durations before crossover are needed to assess their significance. Despite initial reports of efficacy and subsequent FDA approval, the unresolved nature of the issues surrounding VNS for TRMD has resulted in inconsistent insurance reimbursement, and has thus significantly restricted its availability.

ADVERSE EVENTS WITH VAGUS NERVE STIMULATION

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.[91] The infection rates reported in individual clinical trials of VNS for both epilepsy and depression are summarized in Table 3. 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

TABLE 3. *Rates of Common Perioperative and Stimulation-Related Adverse Events with VNS for Epilepsy or Depression*

Series	*N*	Follow-up Period, mo	Adverse Events, no. (%)												
			Infection*	Neck Pain	Other Pain	Voice Alteration	Coughing	Dyspnea	Pharyngitis	Dyspepsia	Dysphagia	Nausea	Vomiting	Headache	Paresthesia
Epilepsy															
Handforth et al.[45] (1998) (LS)	103	3–4	12 (12)		31 (30)	31 (30)	44 (43)	11 (11)	26 (25)	13 (13)		21 (20)	14 (14)	24 (23)	26 (25)
Handforth et al.[45] (1998) (HS)	95	3–4	11 (12)		27 (28)	63 (66)	43 (45)	24 (25)	33 (35)	17 (18)		14 (15)	17 (18)	23 (24)	17 (18)
VNS Study Group[44] (1995) (LS)	60	3	—	7 (12)	16 (27)	1 (2)	5 (8)	1 (2)						5 (8)	2 (3)
VNS Study Group[44] (1995) (HS)	54	3	—	6 (11)	16 (30)	3 (6)	4 (7)	3 (6)						1 (2)	3 (6)
Labar et al.[42] (1998)	5	9	1 (20)			1 (20)	2 (40)	1 (20)							
Lundgren et al.[34] (1998)	16	2.5–3	—	1 (6)		6 (38)		2 (13)							
Vonck et al.[35] (1999)	15	29	—			2 (13)	3 (20)				1 (7)				
Hosain et al.[60] (2000)	13	6	1 (8)	3 (23)		3 (23)	3 (23)								
Wakai and Kotagal[99] (2001)	5	7.5	—	5 (100)	1 (20)	4 (80)	2 (40)								
Frost et al.[61] (2001)	50	6	2 (4)	5 (10)	5 (10)	22 (44)	15 (30)	2 (4)		2 (4)	1 (2)	2 (4)	1 (2)		4 (8)
Scherrmann et al.[52] (2001)	84	16	2 (2)			48 (57)	3 (4)	2 (2)			3 (4)				
Majoie et al.[101] (2005)	16	6	0 (0)			7 (44)	4 (25)				1 (6)				2 (13)
Helmers et al.[102] (2001)	56	6	0 (0)			32 (57)	21 (38)				1 (2)				
Hui et al.[104] (2004)	13	18	—	3 (23)			3 (23)								
Holmes et al.[105] (2004)	16	3–5.25	—	3 (19)		14 (88)	1 (6)				2 (13)				
Hallböök et al.[58] (2005)	15	9	0 (0)	1 (7)		4 (27)		1 (7)							1 (7)
Alexopoulos et al.[57] (2006)	46	36	5 (11)												
Rychlicki et al.[107] (2006)	34	36	—	4 (12)		15 (44)									
Saneto et al.[108] (2006)	63	18	2 (3)					1 (2)							
Kostov et al.[110] (2007)	12	23	0 (0)	3 (25)	1 (8)	3 (25)		3 (25)							1 (8)
Treatment-Resistant Major Depression (Unipolar and Bipolar)															
Rush et al.[84] (2000)	30	0.25	2 (7)	5 (17)	5 (17)	15 (50)	4 (13)	6 (20)	7 (23)	1 (3)	4 (13)	2 (7)		7 (23)	
Sackeim et al.[88] (2001)	60	0.25	3 (5)	10 (17)	9 (15)	33 (55)	10 (17)	9 (15)	8 (13)	6 (10)	8 (13)	4 (7)		13 (22)	4 (7)
Marangell et al.[86] (2002)	29	12	—	2 (7)	0 (0)	6 (21)	0 (0)	2 (7)	0 (0)		1 (3)	1 (3)		1 (3)	
Nahas et al.[85] (2005)	48	24	—	6 (13)		13 (27)	31 (65)	4 (8)							
Rush et al.[90] (2005) (Active)	119	0.25	10 (8)	25 (21)		81 (68)	35 (29)	27 (23)		12 (10)	25 (21)		13 (11)		19 (16)
Rush et al.[90] (2005) (Sham)	116	0.25	2 (2)	12 (10)		44 (38)	11 (9)	16 (14)		6 (5)	13 (11)		6 (5)		12 (10)
Rush et al.[89] (2005)	209	12					13 (6)				8 (4)				8 (4)

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.

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.[92] Voice alteration is most commonly observed in conjunction with stimulation, but may occur postoperatively as a consequence of improper electrode placement, device malfunction, or patient-inflicted traction injury due to device manipulation.[93] Other uncommon complications in the immediate postoperative period include fluid accumulation in the generator pocket, partial left-sided facial paralysis, and Horner's syndrome.[45,52,93,94]

Stimulation-related

Rates of common stimulation-induced adverse events are summarized in Table 3. 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.[91,93] 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.[95,96] 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, though long-term VNS has not been found to produce histologic evidence of nerve injury.[97] Preoperative laryngeal electromyography may be useful in identifying patients at risk for long-term vocal fold or phonation abnormalities.[98] VNS may cause a mild increase in gastric acid output, but does not affect ulcer formation or vital signs.[45,93] 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 equivalent to those of other cohorts undergoing treatment for refractory epilepsy.[51,53]

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.

Given the reported antidepressant effect of VNS, ongoing research is attempting to elucidate its role in the management of TRMD. One randomized controlled trial failed to show a significant improvement in response rate with VNS, but this trial was limited to short-term follow-up. Indeed, open follow-up at 1 year demonstrated a favorable antidepressant response, a finding consistent with observations of cumulative effects of VNS on seizure control and mood enhancement over time. VNS is approved by the FDA for the treatment of both refractory epilepsy and depression, but the available clinical evidence regarding its efficacy in these applications is not equivalent. More than a decade of FDA 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 in the treatment of refractory depression.

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