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Perspective

VNS Therapy in Treatment-Resistant Depression: Clinical Evidence and Putative Neurobiological Mechanisms

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Currently available therapeutic interventions for treatment-resistant depression, including switch, combination, and augmentation strategies, are less than ideal. Observations of mood elevation during vagus nerve stimulation (VNS) therapy for pharmacoresistant epilepsy suggested a role for VNS therapy in refractory major depression and prompted clinical investigation of this neurostimulation modality. The VNS Therapy System™ has been available for treatment of pharmacoresistant epilepsy since 1997 and was approved by the US Food and Drug Administration for treatment-resistant depression in July, 2005. The physiology of the vagus nerve, mechanics of the VNS Therapy System™, and efficacy and safety in pharmacoresistant epilepsy are reviewed. Promising results of VNS therapy for treatment-resistant depression have been forthcoming from both acute and long-term studies, evidenced in part by progressive improvements in depression rating scale scores during the 1st year of treatment with maintenance of response thereafter. VNS therapy is well tolerated in patients with either pharmacoresistant epilepsy or treatment-resistant depression. As in epilepsy, the mechanisms of VNS therapy of treatment-resistant depression are incompletely understood. However, evidence from neuroimaging and other studies suggests that VNS therapy acts via innervation of the nucleus tractus solitarius, with secondary projections to limbic and cortical structures that are involved in mood regulation, including brainstem regions that contain serotonergic (raphe nucleus) and noradrenergic (locus ceruleus) perikarya that project to the forebrain. Mechanisms that mediate the beneficial effects of VNS therapy for treatment-resistant depression remain obscure. Suggestions for future research directions are described.
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INTRODUCTION

Major depression is now recognized as a highly prevalent (Kessler *et al*, 2003), chronic, recurrent (Judd *et al*, 2000), and disabling biological disorder (Michaud *et al*, 2001) with high rates of morbidity and mortality. Indeed, major depression, which is projected to be the second leading cause of disability worldwide by the year 2020 (Michaud *et al*, 2001), is associated with high rates of mortality secondary to suicide and to the now well-established increased risk of death due to comorbid medical disorders, such as myocardial infarction and stroke (Carney and Freedland, 2003; Robinson, 2003). Considerable strides have been made over the past 2 decades in the development of safe and efficacious antidepressants. Although truly novel therapies with mechanisms other than monoamine neurotransmitter reuptake inhibition represent an active area of investigation, they are years away from being clinically available. Unfortunately, up to 50% of patients with depression do not achieve remission with currently available treatments in short-term (ie, 6–8 weeks), double-blind, clinical trials (Rush and Trivedi, 1995; Rush *et al*, 1998).

Therapeutic strategies that are employed for treatment-resistant depression are myriad and include multiple trials of high-dose antidepressants and varying combinations of antidepressants, augmenting agents, psychotherapy, and electroconvulsive therapy (ECT). A large body of evidence supports the acute efficacy of ECT in treatment-resistant depression. However memory loss and the need for repeated treatments to maintain efficacy preclude the use of ECT as a long-term treatment option (Rasmussen *et al*, 2002). Transcranial magnetic stimulation (Kauffmann *et al*,

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2004; Schulze-Rauschenbach *et al*, 2005), stereotactic subcaudate tractotomy (Dalgleish *et al*, 2004; Malhi and Bartlett, 2000), limbic leukotomy (Montoya *et al*, 2002), and deep brain stimulation (Mayberg *et al*, 2005) are other options for treatment-resistant depression that are, to date, still experimental. One novel treatment modality has recently been approved by the US Food and Drug Administration (FDA). Vagus nerve stimulation (VNS) therapy, which is approved in the US and Europe for treatment of pharmacoresistant epilepsy, is now available in the US for treatment-resistant depression.

In this paper, we review the physiology of the vagus nerve and the mechanics of VNS technology. Data supporting the use of VNS therapy in pharmacoresistant epilepsy will be discussed briefly, as will the purported mechanisms underlying efficacy of VNS therapy in this patient population. Following that, we review evidence for the efficacy and safety of VNS therapy of treatment-resistant depression and examine findings from recently completed mechanism of action studies, most of which are preliminary and have been reported as abstracts, not peer-reviewed manuscripts. More detailed descriptions of mechanistic findings will be reported elsewhere. Our understanding of the mechanism of VNS therapy for treatment-resistant depression is in its infancy, and this paper concludes with a discussion of unmet research needs in the field.

THE VAGUS NERVE

The anatomy and physiology of the vagus nerve (cranial nerve X) is complex and until relatively recently, not well characterized. Named from the Latin word for 'wandering,' the vagus nerve exits the cranium through the jugular foramen, continuing distally through the jugular and nodose ganglia after which it travels between the jugular vein and carotid artery and from there to the larynx, esophagus, trachea, gastrointestinal organs, heart, and aorta. The vagus nerve consists of both efferent and afferent fibers. The parasympathetic efferent fibers provide autonomic regulation of the pharynx, larynx, esophagus, heart, aorta, and most gastrointestinal organs. Some of the efferent fibers in the right vagus nerve regulate heart rate. Somatomotor efferents to the vocal cords and other laryngeal striated muscles consist of highly myelinated, rapidly conducting components of the cervical vagus nerve, in contrast with the unmyelinated, slowly conducting parasympathetic efferents. Afferent fibers of the vagus nerve carry sensory information from the head, neck, abdomen, and thorax to the dorsal medullary complex, in particular the NTS. The perikarya of the vagal afferent fibers are located in the nodose ganglion. Approximately 80% of the nerve fibers in the cervical vagus nerve are afferent fibers (Figure 1).

The left vagus nerve bifurcates on entering the medulla to innervate the NTS bilaterally, but only synapses ipsilaterally on the other nuclei of the dorsal medullary complex of the vagus. The NTS relays information to other brain regions via direct projections to the parabrachial nucleus (PBN), the cerebellum, the raphae, the periaqueductal gray (PAG), and the locus coeruleus, as well as ascending secondary projections to limbic, paralimbic, and cortical regions (Figures 2 and 3). Thus, the vagus nerve provides information to the brain in a bottom-up manner. The PBN is the structure that relays information from the NTS directly to the hypothalamus, thalamus, amygdala, and nucleus of the stria terminalis. Subsequently, the thalamus relays information to the insular, orbitofrontal, and prefrontal cortices, and other higher brain structures. Vagal projections to the locus ceruleus and raphe nuclei are important because they contain the perikarya of noradrenergic and serotonergic projections, respectively, that are implicated in the mechanism of action of traditional antidepressants (Lenox and Frazer, 2002). It is not known if vagus input to these individual regions are excitatory or inhibitory.

Projections from the NTS reach structures that are associated with the regulation of mood and emotion, seizure activity, anxiety, intestinal activity, satiety, and pain perception (Figures 2 and 3; see Berthoud and Neuhuber,

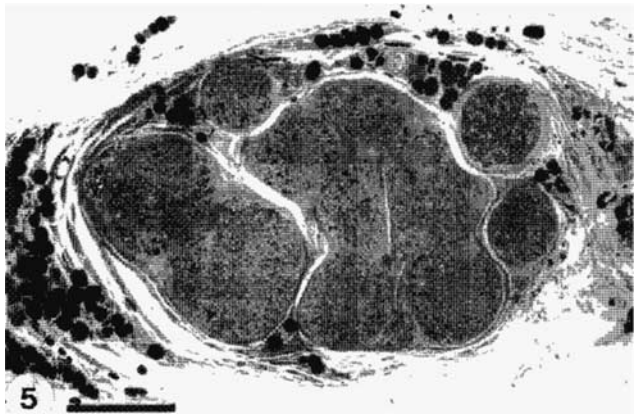

Figure 1 The human vagus nerve contains approximately 100 000 axons, 80% of which are unmylienated afferent sensory and visceral fibers.

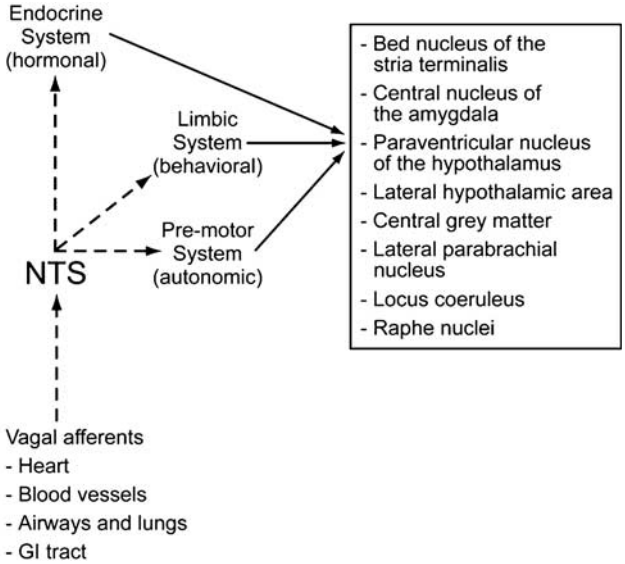

Figure 2 Vagal afferents from the viscera project initially to the NTS and from there affect hormonal, autonomic, and behavioral systems, which are thought to be influenced via secondary projections to higher brain structures.

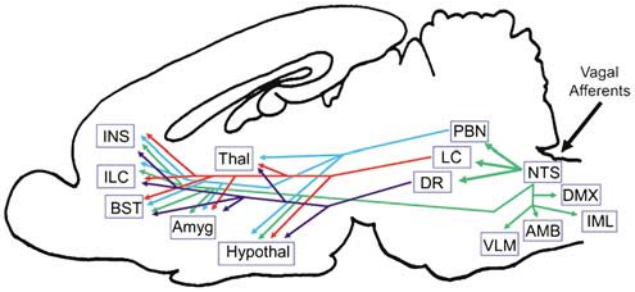

Figure 3 Limbic and cortical regions of the brain receive vagal afferents by multiple, overlapping routes. NTS = nucleus tractus solitarius; AMB = nucleus ambiguous; DMX = dorsal motor nucleus of the vagus; IML = intermediolateral column of spinal cord (symp pregang); VLM = ventrolateral medulla; Amyg = amygdala; INS = insular cortex; ILC = infralimbic cortex; BST = bed nucleus of stria terminalus; PBN = parabrachial nucleus; DR = dorsal raphe; LC = locus ceruleus; Thal = thalamus; Hypothal = hypothalamus. Green lines (tracts from the NTS); blue lines (tracts from the DR); red lines (tracts from the LC); light blue lines (tracts from the PBN). Courtesy of J Thomas Cunningham, University of Texas Health Science Center at San Antonio.

2000; George *et al*, 2004, 2000a, b; Henry, 2002 for extensive reviews). The vagus nerve is now believed to be involved in nociception by relaying sensory information from the gastrointestinal and respiratory systems to higher brain regions as well as by mediating the affective-emotional response to pain (Berthoud and Neuhuber, 2000). Moreover, lamina I spinal neurons that mediate feelings of pain, temperature, and other physiological sensations project directly to the medulla, NTS, PBN, and PAG, and secondarily to the hypothalamus and limbic–cortical regions along a pathway that is similar to the afferent projections of the vagus nerve (Craig, 2002).

MECHANICS OF VNS

The VNS device consists of an implantable generator that is connected to electrodes which deliver low-frequency, chronic intermittent-pulsed electrical signals to the left cervical vagus nerve. The VNS Therapy System™ is commercially available for treatment of pharmacoresistant epilepsy and treatment-resistant depression (Cyberonics Inc., Houston, TX). The multiprogrammable pulse generator, which is roughly the size of a pocket watch, is implanted subcutaneously in the anterior chest wall during an outpatient surgical procedure similar to implantation of a cardiac pacemaker. Through a separate incision in the neck, the surgeon wraps the bipolar nerve-stimulating electrodes around the left cervical vagus nerve. Subsequently, the electrodes are connected to the implanted generator via a subcutaneous tunneling procedure (George *et al*, 2004; Matthews and Eljamel, 2003).

Clinicians are able to adjust stimulation parameters (ie, the 'dose') noninvasively with a telemetric wand that is linked to a hand-held personal digital assistant (Figure 4). Using the wand, the clinician can adjust the stimulation parameters, such as intensity, frequency, pulse width, and duty cycle (ie, duration of stimulation ('on' time) and interval between stimulation ('off' time)). The telemetric wand can be used to trigger a single duty cycle. Telemetric linkage also enables retrieval of data for further assessment

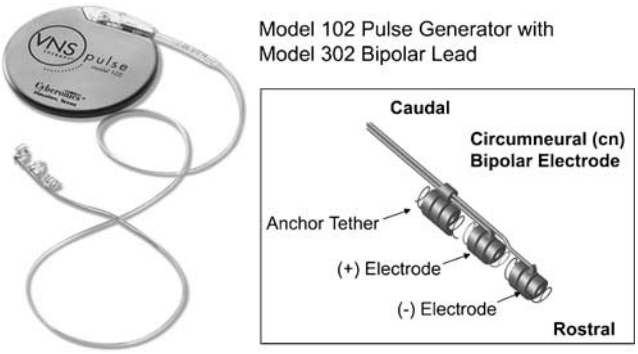

Figure 4 The VNS Therapy™ System.

of the effects of VNS therapy. Mechanical and electrical devices are built into the system as safety features to prevent high-frequency stimulation. In addition, patients are supplied with a magnet that can be held over the generator to temporarily suspend stimulation. Programmed stimulation resumes when the patient removes the magnet that, if needed, allows control over side effects (George *et al*, 2004; Matthews and Eljamel, 2003).

PHARMACORESISTANT EPILEPSY

The VNS Therapy System™ (Cyberonics Inc., Houston, TX) has been available in Europe since 1994 and in the United States since 1997 for the reduction of seizure frequency in patients with medically refractory, partial-onset seizures. There is extensive clinical experience with VNS therapy in this patient population. Over 30 000 patients with epilepsy have received VNS therapy for an accumulated experience of 79 000 patient years. The VNS Therapy System™ software enables a wide range of stimulation parameters, which consist of frequency (1–30 Hz), intensity (0–3.5 mA), duty cycle (7–60 s on: 12 s–180 min off), and pulse width (130–1000 μs). Typical initial stimulation parameters used in patients with epilepsy are 30 Hz, 0.1–1.0 mA, 30 s on : 5 min off, and 500 μs. Stimulation parameters are typically titrated after several months' time to higher current outputs (eg, 1.0–2.0 mA) and greater duty cycles (eg, 30 s on : 1.1 min off). Optimal stimulation parameters for VNS therapy in patients with pharmacoresistant epilepsy are not known, and individual patient characteristics guide the adjustments needed for a given clinical situation.

Efficacy and Safety in Epilepsy

The results of two prospective, randomized, double-blind studies of over 300 patients established the acute efficacy of VNS therapy of intractable seizures. A total of 313 patients were randomized to receive 12 or 14 weeks of high (30 Hz, 30 s on/5 min off; 500 μs pulse width) or low stimulation (1 Hz, 30 s on/90–180 min off; 130 μs pulse width) (Ben-Menachem *et al*, 1994; Handforth *et al*, 1998; The Vagus Nerve Stimulation Study Group, 1995). Reductions in seizure frequency were greater for the high stimulation groups (24.5% in the first study; 28% in the second study) than for the low stimulation group (6.1 and 15%, respectively; $P \leqslant 0.04$ in both studies). VNS therapy was well tolerated. Adverse events were voice change, which was

the most often reported adverse event, and dyspnea, cough, parasthesias, and infection or pain at the implantation site. Adverse effects on cognition, motor control, cardiac function, or gastrointestinal function did not occur more often in VNS therapy groups than in control groups.

Findings from open-label extensions of five short-term studies, including the two summarized above, demonstrate a sustained or improved level of seizure reduction and tolerance to adverse events (454 patients). Patients in the high stimulation groups continued to receive treatment with the same stimulation parameters, and patients treated with low stimulation were crossed over to high stimulation. Long-term VNS therapy resulted in a 35% reduction in seizure frequency at 1 year, 44.3% at 2 years, and 44.1% at 3 years. The proportion of patients with sustained seizure frequency reductions of 50% or greater was 23% at 3 months, 36.8% at 1 year, 43.2% at 2 years, and 42.7% at 3 years. Thus, it appears that the acute, 3-month response increases up to the 2nd year of treatment after which response rates tend to plateau (DeGiorgio *et al*, 2000; Morris *et al*, 1999; Salinsky *et al*, 1996). Moreover, response during acute treatment predicted maintenance of response at 1 year (Salinsky *et al*, 1996). Long-term treatment was well tolerated, with continuation rates of 96.7% at 1 year, 84.7% at 2 years, and 72.1% at 3 years (Morris *et al*, 1999).

Mechanism of Anticonvulsant Action

The mechanisms underlying the efficacy of VNS therapy for pharmacoresistant epilepsy are not known with precision, in part because the pathophysiology of epilepsy itself is incompletely understood. Indeed, one cannot speak of 'one' pathophysiology of epilepsy anymore than one can speak of 'one' pathophysiology of mood disorders. There are multiple causes of both disorders, each with subtypes that are characterized by distinct pathophysiology.

Seizures are characterized by synchronous firing of populations of neurons in the central nervous system, which is an observation that led to the hypothesis that VNS therapy converts synchronous cortical activity to desynchronous activity. Hammond *et al* (1992) tested this hypothesis in an open-label study of nine adults with intractable complex partial seizures. Acute VNS did not reduce focal spiking on the EEG during interictal periods. However, stimulation during the aura or shortly after the onset of an ictal episode was associated with reduced synchronous discharges (spiking) that, as speculated by the authors, prevented or interrupted the seizure.

Some have speculated that VNS therapy results in a global reduction in cortical excitability. Preliminary findings that were presented at the American Epilepsy Society 56th Annual meeting showed that VNS-implanted patients with epilepsy exhibited a higher resting motor threshold during activation of VNS compared to after the device was off for 30 min. The investigators interpreted these results to suggest that VNS may be associated with a reduction in motor cortex excitability (Dean *et al*, 2001). Nonetheless, the effects and implications of VNS therapy-related reductions in the synchronization of specific neural circuits are not known.

Technical challenges have hampered a systematic analysis of the mechanisms of VNS in animal models of seizures and epilepsy. The difficulty inherent in attaching electrodes to the very small vagus nerves of mice and rats is one limiting factor. In addition, the small size of these animals necessitates use of external generators that can provide short-term intermittent stimulation, but not chronic intermittent stimulation (George *et al*, 2004).

While systematic analysis of the mechanisms by which VNS therapy suppresses seizures has not been undertaken, several considerations support the hypothesis that seizures are controlled by regulating the efficacy of diffusely projecting afferents to the forebrain, such as the serotonergic or noradrenergic projections from the raphe and locus ceruleus, respectively. More specifically, VNS therapy is posited to control seizures arising from multiple cortical sites, which suggests that the sites at which VNS therapy controls neuronal excitability are widely distributed in the neocortex and archicortex. Furthermore, VNS therapy does desynchronize EEG recorded from electrodes widely distributed over the scalp, an effect that is consistent with regulating the efficacy of a population of diffusely projecting afferents. Widespread increases in blood flow in the hypothalamus, thalamus, insular cortex, and cerebellum and reduced blood flow in the hippocampus, amygdala, and posterior cingulate gyrus within 18 h of beginning VNS therapy in patients with partial epilepsy are consistent with the idea of widespread effects of VNS therapy on neuronal activity (Henry *et al*, 1998). Acute increases in thalamic blood flow during VNS therapy correlated with chronic reductions in seizure frequency (Henry *et al*, 1999). After chronic VNS therapy in the same cohort of patients, VNS therapy continued to increase blood flow in the same subcortical regions that had been activated acutely, but cortical regions showed much less activation on PET studies after chronic compared to acute VNS therapy (Henry *et al*, 2004). Similar to the imaging–efficacy correlations noted at acute VNS activation on PET, increased blood flow in the thalamus during chronic VNS therapy correlated with chronic reductions in seizure frequency. Bilateral thalamic activation as defined by increases in blood flow during VNS appears to be a marker of antiseizure effects, but the cellular and molecular mechanisms that underlie this correlation are unknown.

Given the powerful innervation of the NTS by vagal afferents, one important question is whether regulating the excitability of NTS neurons can affect seizure threshold. Interestingly, Walker *et al* (1999) examined the effects of intra-NTS microinjections of agonists or antagonists of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) and the excitatory neurotransmitter, L-glutamate, on seizure activity induced by bicuculline infusion into pyriform cortex. Administration of the GABA receptor agonist, muscimol, or the glutamate receptor antagonist, kynurenine, attenuated chemically induced seizures. Together these findings suggest that reducing the activity of neurons in NTS somehow suppresses limbic seizures and provides a valuable clue as to neural circuits mediating the antiseizure effects of VNS therapy. To date, there are no imaging data that correlate with these findings.

The antiseizure effects of reduced NTS neuronal activity raises the question of potential monosynaptic or polysynaptic targets that may mediate the anticonvulsant properties of VNS therapy. Two attractive candidates are the pars

reticulata neurons of the substantia nigra (McNamara *et al*, 1984) and the raphe serotonergic neurons (Kovacs and Zoll, 1974; Siegel and Murphy, 1979). Suppressing the firing of zona reticulate substantia nigra neurons or increasing the firing of raphe neurons leads to elevated seizure thresholds, the former increasing focal thresholds for seizures evoked in olfactory bulb, amygdala, or entorhinal cortex (McNamara *et al*, 1984). How VNS therapy regulates the activity of NTS neurons and whether and how VNS therapy and manipulations of NTS regulate the activity of substantia nigra and raphe serotonergic neurons warrants future study.

TREATMENT-RESISTANT DEPRESSION

The rationale for studying VNS therapy in treatment-resistant depression was based on several different observations. Direct evidence supporting a role for VNS therapy in depression came from early observations of mood improvement in patients with epilepsy who participated in early VNS studies. Following these initial observations, patients with epilepsy were evaluated prospectively with standard depression symptom severity rating scales, which revealed that VNS therapy was associated with statistically significant improvements in mood that were not related to reductions in seizure frequency (Elger *et al*, 2000; Harden *et al*, 2000). In addition, several different lines of indirect evidence prompted further study of VNS therapy in depression. For example, PET imaging during VNS therapy of epilepsy demonstrated reductions in the metabolic activity of the amygdala, hippocampus, and cingulate gyrus (Henry *et al*, 1998), structures involved in regulating mood. These brain regions also are implicated during PET imaging in depressed patients who are being treated with antidepressants (Drevets *et al*, 2002; Mayberg *et al*, 2000; Nobler *et al*, 2001). Hippocampal involvement during VNS therapy also is consistent with the findings of studies showing increased expression of brain-derived neurotrophic factor (BDNF) in animal models of depression (Nibuya *et al*, 1995). The documented efficacy of anticonvulsants, such as carbamazepine, lamotrigine, valproate, and perhaps others, as mood stabilizers and/or antidepressants in bipolar disorder (Yatham, 2004) and the anticonvulsant properties of ECT (Kellinghaus *et al*, 2003; Lisanby *et al*, 2001) are concordant with the hypothesis that VNS therapy may be a useful therapeutic option for depression. Other findings that suggest a role for VNS therapy of depression include the effect of VNS therapy on brain regions associated with the norepinephrine (Krahl *et al*, 1998; Naritoku *et al*, 1995) and serotonin neural systems (Ben-Menachem *et al*, 1995), long thought to be important in the pathophysiology of depression. In addition, VNS has been shown to be as effective as ECT or desipramine in an animal model of depression (ie forced-swim test) (Krahl *et al*, 2004).

In 2001, the VNS Therapy™ System (Cyberonics Inc., Houston, TX) was approved for use in patients with treatment-resistant or treatment-intolerant major depressive episodes, including unipolar depression and bipolar disorder in Canada and the European Economic Area. To date, over 342 patients with treatment-resistant depression have received VNS therapy, with 777 patient years of cumulative clinical experience. Prior to the recent FDA approval of VNS therapy, the only approved medical device that was used in treatment-resistant depression was ECT. In accordance with the FDA Modernization Act of 1997, approval for treatments that address unmet medical needs are eligible for fast-track approval (eg antiretroviral agents for HIV infection). Consequently, FDA expedited approval for VNS therapy because of the lack of approved drug treatments and concerns about long-term efficacy and safety of ECT. Manufacturers of treatments approved via the fast-track process are required to conduct adequate follow-up studies to further characterize efficacy and safety. Such follow-up studies are ongoing for VNS therapy in patients with treatment-resistant depression.

As a prelude to the following review of VNS therapy for treatment-resistant depression, it is relevant to briefly compare and contrast FDA approval standards for drugs and devices. In their goal to expedite availability of new device technologies without compromising scientific integrity in the decision-making process, FDA has adopted the 'least burdensome concept' guidelines (CDRH, 2002), which is considered a successful means of addressing premarket issues that involves the smallest investment of time, effort, and resources on the part of the applicant and FDA. The least burdensome concept guidelines apply to all devices regulated by FDA.

Study design is an especially salient issue in the context of the FDA approval process. Approval of a new drug requires evidence of efficacy and safety from two positive, randomized, placebo-controlled trials. However, FDA requires a different standard of efficacy and safety evidence for medical devices in accordance with the least burdensome concept guidelines. Indeed, 55% of newly approved device applications are supported by data from nonrandomized clinical trials (Kahan, 2000). Difficulties in maintaining the study blind, which is a methodological challenge inherent in trials of medical devices, is a major concern for the design of device studies. The VNS therapy system requires an invasive surgical procedure to implant the device. Use of traditional placebo controls is neither applicable nor ethical under these circumstances, which lead to acceptance by the FDA of studies using sham controls, as in the VNS therapy trials (Demitrack, 2005). Therefore, the findings of medical device trials, including VNS therapy, should be interpreted with the understanding that, by design, they do not include a placebo arm. Many medical device trials involve before and after comparisons or comparison to historical controls.

Short-Term Efficacy

The acute effects of VNS therapy for treatment-resistant depression have been studied in a 10-week pilot study ($N=60$, Rush *et al*, 2000; Sackeim *et al*, 2001a) and in a larger, double-masked, sham-controlled, 10-week registration trial ($N=235$, Rush *et al*, 2005a). Of the 59 eligible patients in the pilot study, 30.5% ($N=18$) were responders (ie, $\geqslant$50% reduction in baseline HAMD-28 total score), and 15.3% remitted ($N=9$; HAMD-28 total score $\leqslant$10). Clinically meaningful improvement was gradual, with a mean time to response of 48.1 days. VNS therapy was well tolerated, and none of the 60 patients withdrew from the study because of adverse events.

The larger study was designed to compare VNS therapy with sham treatment in patients with treatment-resistant unipolar depression or depressed-phase, bipolar disorder (Rush *et al*, 2005a). This was a severely ill cohort, with a mean baseline HAMD-24 score of 29.2 and a mean duration of 49.1 months for the current episode. All patients were maintained for at least 4 weeks on a stable medication regimen before the preimplantation baseline assessment, and medications were not changed for the duration of the 12-week study. There were 112 patients in the treatment group, and 110 patients served as sham controls. The VNS therapy device was activated in the treatment group following a 2-week, single-blind recovery period after implantation. Stimulation parameters were adjusted within predetermined levels until the 3rd week postactivation when parameters were fixed for the remaining 8 weeks of the study. Median stimulation parameters at end point were 0.75 mA (intensity), 20 Hz (frequency), 500 μs (pulse width), 30 s (time on) : 5 min (time off). Although VNS therapy was very well tolerated, short-term efficacy was not demonstrated. Response rates, defined as $\geqslant$50% reduction in baseline HAMD-24, for the active treatment and sham control groups were 15.2 and 10.0%, respectively ($P = 0.251$; LOCF).

Long-Term Efficacy

Evidence suggesting progressive improvements in seizure control in patients with pharmacoresistant epilepsy provided the rationale for long-term study of VNS therapy for treatment-resistant depression. The 59 patients who completed the short-term pilot study (Rush *et al*, 2000; Sackeim *et al*, 2001a) and met response criteria at 3 months (early responders) or 1 year (late responders) were followed for a total of 2 years (Nahas *et al*, 2005). The 3-month response rates of 30.5% increased to 44.1% at 1 year and remained at that level (42.4%) at the 2-year time point (Nahas *et al*, 2005). Sackeim and colleagues presented data from this cohort at the 43rd Annual Meeting of the American College of Neuropsychopharmacology showing that when maintenance of response was considered, 55.6% of early responders and 78.6% of late responders continued to be responders at 2 years (Sackeim *et al*, 2004). Rates of remission in a subset of 30 patients, defined as $\leqslant$10 on the HAMD-28, increased from 17% at 3 months (five of 30 patients) to 29% at 1 year (eight of 28 patients; $P = 0.045$) (Marangell *et al*, 2002).

One-year naturalistic follow-up of 205 patients who completed the short-term registration trial (Rush *et al*, 2005a) revealed a similar pattern of later, but sustained response (Rush *et al*, 2005b). Patients in the active treatment group continued on VNS therapy for an additional 9 months, for a total of 12 months. Patients randomized to the sham control group in the short-term study (Rush *et al*, 2005a), were crossed over to a 12-month course of active VNS therapy (Rush *et al*, 2005b). In addition to VNS therapy, all patients continued to receive treatment as usual (TAU). At LOCF end point, the response rate was 27.2, and 15.8% of patients remitted. Rates of response and remission doubled between 3 and 12 months of treatment ($P < 0.005$), indicating progressive clinical improvement after the initial 3 months of VNS therapy. Similar results were noted for the secondary clinical end points. Although direct, comparative studies are not available, the long-term benefits of VNS therapy compare favorably to ECT, in which a substantial majority of patients relapse within 6 months of achieving remission (Prudic *et al*, 2004; Sackeim *et al*, 2001b).

Data from the 205 patients who completed the 12-month naturalistic study (Rush *et al*, 2005b) were compared with a matched control group of 124 patients with treatment-resistant depression who received only TAU (George *et al*, 2005). The primary outcome measure was the difference in Inventory of Depressive Symptomatology Self-Report scores ($IDS\text{-}SR_{30}$) per month between the VNS therapy plus TAU and the TAU groups. At end point, VNS therapy plus TAU was associated with a mean improvement on the $IDS\text{-}SR_{30}$ score of 9.3 points, which represented a significantly greater improvement than TAU (4.2-point improvement; $P < 0.001$). Differences in LOCF response rates between VNS therapy plus TAU (19.6%) and TAU (12.1%) did not achieve statistical significance ($P = 0.108$). In contrast, LOCF remission rates were significantly greater in the VNS therapy plus TAU group (13.2%) compared to TAU (3.2%; $P = 0.007$). Although these results are promising, extrapolation of the 1-year findings to clinical practice may be limited because the TAU group was not randomized and the TAU therapies were not restricted in either group after the first 3 months.

Mechanism of Action in Treatment-Resistant Depression

As with epilepsy, the mechanisms by which VNS therapy may benefit treatment-resistant depression are presently unclear. Different methodological approaches have been employed in an effort to better understand the mechanism of action of VNS therapy, such as mapping neural substrates and identifying changes in neurotransmitter systems during VNS therapy in patients with treatment-resistant depression.

Mapping neural substrates. Expanding on earlier findings (Naritoku *et al*, 1995), Kling *et al* (2003) measured expression of the protein encoded by the immediate early gene *c-fos*, which is a marker of neuronal activity, in rats exposed to short-term VNS or sham conditions. Their preliminary findings were presented at the 58th Annual Scientific Convention of the Society of Biological Psychiatry (Kling *et al*, 2003). Compared to control animals, VNS resulted in markedly increased *c-fos* expression in forebrain (lateral hypothalamus, paraventricular nuclei, CA3 hippocampal fields, and neocortex) and brain stem regions (NTS, nucleus raphe magnus, PBN, A7 area, locus ceruleus, and periaqueductal gray). These findings support the idea that VNS therapy acts directly by stimulating brain stem structures and indirectly by regulating the activity of neurons in limbic and cortical regions involved in mood regulation (Figures 2 and 3).

Functional neuroimaging studies in patients with treatment-resistant depression using SPECT, PET, or functional magnetic resonance imaging (fMRI) have been conducted to identify discrete brain regions that are affected by VNS therapy. This is an emerging literature that, at present, is difficult to interpret (Chae *et al*, 2003). The heterogeneity in

imaging methods, small sample sizes, assorted diagnoses (eg unipolar major depression; bipolar disorder), varying types of antidepressant therapies, and different timeframes during which scans were obtained preclude definitive conclusions about this literature. In addition, none of the imaging studies have yet been replicated. Some findings appear to be similar to VNS therapy of pharmacoresistant epilepsy, while others demonstrate functional changes that may be unique to VNS therapy in patients with treatment-resistant depression, a subset of which are comparable to findings of antidepressant studies. Despite these limitations, the findings of recent imaging studies conducted after acute or during long-term VNS therapy in patients with treatment-resistant depression represent an important first step in elucidating the mechanisms of VNS therapy. The effects on medial temporal structures are of particular interest, given that such structures are theoretically important to both epilepsy and depression and have been implicated in the *c-fos* work in rats (Kling *et al*, 2003; Naritoku *et al*, 1995).

SPECT imaging studies: Findings from two SPECT imaging studies of patients with treatment-resistant depression have been reported. In their presentation of preliminary data from 11 patients with treatment-resistant depression at the 40th Annual Meeting of the ACNP, Devous and colleagues concluded that, compared with normal controls, a 10-week course of VNS therapy was associated with resolution of some of the regional cerebral blood flow (rCBF) abnormalities in limbic and cortical structures (eg insula, dorsolateral prefrontal cortex (DLPFC), temporal cortex) that are associated with depression. Of note, thalamic rCBF after 10 weeks was increased compared to controls (Devous *et al*, 2002). Two patients were responders and five were partial responders after 10 weeks of VNS therapy. Medial temporal findings of interest include decreased hippocampal rCBF at baseline in patients compared to controls and a correlation between HAMD scores and increased medial temporal cortex rCBF in patients after 10 weeks of VNS therapy. Changes seen in the anterior cingulate were inversely correlated with 6-month HAMD scores ($n = 11$) (Devous *et al*, 2002).

Zobel *et al* (2005) reported the findings of SPECT imaging in 12 patients with treatment-resistant depression at baseline and after 4 weeks of VNS therapy. All patients were maintained on their antidepressant regimens during the study. Compared to baseline, a 4-week course of VNS therapy resulted in increased rCBF in the left middle frontal gyrus (BA 46) and reduced rCBF in the hippocampus/amygdala, left caudate, dorsal brainstem, and other areas via statistical parametric mapping (SPM) analyses. Region of interest (ROI) analyses demonstrated significant reductions in the right DLPFC, left subgenual cingulate, bilateral ventral anterior cingulate, right dorsal anterior cingulate, bilateral amygdala, left hippocampus, right thalamus, left caudate, and the brainstem. Changes in the right hippocampus trended toward significance. Medial temporal findings in this study included reduced rCBF in the amygdala and left hippocampus by both the SPM and ROI analyses at 4 weeks compared to baseline.

PET imaging studies: Results of ^{18}F-fluorodeoxyglucose (FDG) PET imaging studies from two different centers have been presented. Conway and colleagues reported preliminary PET findings at the 57th Annual Scientific Convention of the Society for Biological Psychiatry from seven patients with treatment-resistant depression who were scanned prior to VNS activation and again after 12 weeks of VNS therapy. They observed increased metabolic activity in the orbitofrontal cortex, amygdala, parahippocampal gyrus, insula, and cingulate gyrus. In this study, the medial temporal findings consisted of increased metabolic activity in the left parahippocampal gyrus. Unlike the SPECT study by Zobel *et al* (2005), reductions in activation of these regions were not noted (Conway *et al*, 2002).

In contrast, findings of widespread reductions in midbrain glucose metabolism were observed by another group of investigators in a preliminary study of chronic VNS therapy of treatment-resistant depression that was presented at the 58th Annual Scientific Convention of the Society of Biological Psychiatry (Hagen *et al*, 2003; Sheikh *et al*, 2003). After a 1-year course of VNS therapy in eight patients, decreased metabolism compared to baseline was noted in the substantia nigra, ventral tegmentum, hypothalamus, middle and inferior frontal gyrus, insula/claustrum, and superior temporal gyrus. Increased glucose metabolism compared to baseline occurred in the cerebellum, precuneus-BA7, fusiform gyrus-BA37, and medial frontal-BA6 (Sheikh *et al*, 2003). In this same cohort, five patients exhibiting improvement at 1 year showed greater increases in metabolism in the occipital and temporal lobes, middle frontal gyrus, and inferior frontal gyrus and greater reductions in the midbrain (substantia nigra, ventral tegmentum), cerebellum, posterior cingulate, medial frontal/pregenual cingulate, and hippocampus compared to three patients who did not improve (Hagen *et al*, 2003). Relevant medial temporal findings include decreased FDG metabolism at 1 year in the left hippocampus of patients whose depression improved during VNS therapy *vs* patients who did not respond.

BOLD fMRI studies: A feasibility study of blood oxygenation level (BOLD) fMRI in nine patients with treatment-resistant depression who were chronically treated with VNS and antidepressants also revealed changes in brain function (Bohning *et al*, 2001). The BOLD fMRI signal is thought to be analogous to rCBF changes seen with SPECT and PET (Casey, 2000), but this is not entirely certain. The BOLD fMRI changes in these patients following a stimulation cycle of 13 s on and 103 s off consisted of bilateral activation of the orbitofrontal and parieto-occipital cortex and activation of the left temporal cortex (as reported by Devous *et al*, 2002), the left amygdala (as reported by Conway *et al*, 2002), and the hypothalamus (in contrast to findings of Sheikh *et al*, 2003).

Summary of medial temporal imaging findings: Despite the heterogeneity of methods and the overall lack of statistical power, it is nonetheless striking that each imaging study revealed changes in medial temporal structures. Changes were observed in the amygdala in some studies and in the hippocampus or parahippocampus in others. In addition, medial temporal changes were sometimes bilateral, and in some studies, changes were limited to the left medial temporal regions. Moreover, some, but not all, of the studies showed decreases in medial temporal rCBF or FDG metabolism (over varying time points). Clearly, future studies are needed to better characterize changes in these

brain regions. A study with a sufficiently large patient sample that provides adequate power should help determine if changes are bilateral or lateralized and which temporal structures are involved and which are not.

Identifying neurotransmitter systems. Studies have been conducted recently to identify the effects of VNS therapy on neurotransmitter systems. In one study, 21 patients with treatment-resistant depression who were participating in a clinical trial of VNS therapy consented to undergo cerebrospinal fluid (CSF) collections at postimplantation (baseline) and again after 12 and 24 weeks of treatment (Carpenter *et al*, 2004). Ten of the patients served as sham subjects for 12 weeks, after which they were crossed over to active VNS therapy. The CSF samples were assayed for concentrations of norepinephrine, 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), 3-methoxy-4-hydroxyphenylglycol, and GABA. Compared to sham conditions, active VNS therapy was associated with significantly elevated CSF concentrations of HVA, but no changes in the other substrates. An increased ratio of HVA : 5-HIAA levels correlated with clinical improvement with VNS therapy.

The SSRIs are believed to exert their antidepressant effect in a two-stage process: first, SSRIs increase 5HT concentrations by blocking 5HT reuptake, increasing the occupancy of the $5HT_{1A}$ autoreceptors by 5HT, decreasing the firing rate of the serotonin neurons, and inhibiting serotonin release; and second, by eventually downregulating the autoreceptors and promoting release of serotonin from the presynaptic neuron (Lenox and Frazer, 2002). Serotonin is densely concentrated in dorsal raphe nucleus neurons in the midbrain. The effects of VNS on the firing rates of dorsal raphe serotonergic neurons in rats exposed to acute and chronic VNS or sham stimulation were described in a preliminary report presented at the Society for Neuroscience Annual Meeting (Debonnel and Dorr, 2004). Unlike SSRIs, VNS was not associated with an initial reduction in the firing rates of serotonergic neurons. Rather, raphe neuron firing rates progressively increased over 2 weeks (Debonnel and Dorr, 2004), which is consistent with the progressive increase in antidepressant response observed in clinical studies of VNS therapy and with antiseizure effects of serotonin (Clinckers *et al*, 2004). Also of interest was the finding that VNS therapy did not result in downregulation of the $5HT_{1A}$ autoreceptors, suggesting that VNS therapy alters serotonin availability by a mechanism that is distinct from the SSRIs.

UNMET RESEARCH NEEDS

One key limitation to the general study of treatment-resistant depression is the lack of a validated and universally accepted definition of treatment resistance. Currently, treatment history and the duration, recurrence, and severity of depressive episodes form the boundaries of 'treatment resistance.' In the not too distant future, it is reasonable to expect that subtypes of treatment resistance will be defined in neurobiological terms in the same way that various causes of refractory hypertension, such as pheochromocytoma, have been identified. Expression of genetic polymorphisms in the serotonin transporter, MRI evidence of white matter hyperintensities, hippocampal volume reduction, regional imaging markers (eg subgenual cingulate and thalamic hyperactivity), and neuroendocrine data (eg salivary cortisol levels) represent only a few of the possible parameters on which to base a biological definition of treatment-resistant depression.

Our understanding of the neurobiological mechanisms of VNS therapy is just beginning to take shape. This novel technology offers a new treatment modality for the most seriously ill of the sizable depressed patient population and provides a unique opportunity to further our understanding of the pathophysiology of depression. As the field moves forward, a general research model is needed to meet the dual goals of elucidating the mechanism of action of VNS therapy and improving clinical outcomes. Preclinical research should initially focus on a comprehensive description of the brain areas affected by VNS (ie its functional neuroanatomy) and the effects of different stimulation parameters. Clinical studies should build on the findings of work in animal models and further investigate optimal stimulation parameters (ie dosing studies), the role of VNS therapy in different patient populations, and the identification of biomarkers of risk and response. Some specific preclinical and clinical research questions related to mechanism of action/pathophysiology and clinical efficacy include:

Mechanisms/Pathophysiology

- What are the cellular and molecular mechanisms by which VNS elevates seizure threshold in animal models of epilepsy?
- In the absence of an animal model for treatment-resistant depression, is VNS effective in animal models of depression? Laboratory animal studies, including those in non-human primates, should take full advantage of contemporary methods to determine the effects of VNS on a variety of neurotransmitter systems and on synaptic plasticity.
- Does chronic VNS in laboratory animals produce effects that are similar to the SSRIs, selective norepinephrine reuptake inhibitors, ECT, and other antidepressant treatments, such as changes in BDNF and increased hippocampal neurogenesis?
- How do the effects of acute and chronic VNS therapy of treatment-resistant depression differ? Does chronic VNS therapy induce synaptic plasticity?

Clinical Outcome

- What are the optimal stimulation parameters of VNS for elevation of seizure threshold in animal models of epilepsy?
- Is it possible to identify surrogate markers of VNS (eg, fMRI, PET, neuroendocrine data) that correlate with maximally elevated seizure threshold in animal models of epilepsy?
- Are stimulation parameters that are optimal for the treatment of epilepsy also optimal for the treatment of depression?
- What are the optimal stimulation parameters of VNS therapy for response and remission of treatment-resistant depression?

- How do the stimulation parameters and the time course of imaging findings relate to the observed delays in therapeutic response?
- What is the relationship between stimulation parameters and regional brain changes in responders *vs* nonresponders?
- Considering the fact that all of the VNS depression treatment trials were conducted in patients who were maintained on existing psychopharmacologic regimens, to what extent does VNS therapy augment the behavioral and neurobiological effects of currently available antidepressants and anticonvulsants?
- Can predictors of response to VNS therapy in depressed patients be identified by functional imaging or genetic studies?
- Would modifications in stimulation parameters, such as higher frequencies or longer pulse widths, target different brain regions and possibly uncover biological markers for response or nonresponse in treatment-resistant depression?

The need for hypothesis-driven clinical studies specifically designed to identify stimulation parameters during VNS therapy of treatment-resistant depression that optimize remission rates remains a high priority. Ideally, stimulation parameters should first be identified in animal models; such studies are ongoing. Once optimal stimulation parameters are identified, they should be correlated with changes on functional imaging scans. BOLD fMRI has been used to determine if there is a dose–response of different stimulation parameters during VNS therapy of treatment-resistant depression (Lomarev *et al*, 2002; Mu *et al*, 2004). Thus far, a pulse width of 250 μs results in the same degree of global activation as a 500 μs pulse width. Moreover, a pulse width of 130 μs is not sufficient for immediate activation of some brain regions (Mu *et al*, 2004). A similar study was conducted to determine the effects of different stimulation frequencies on brain activation. A higher frequency of stimulation (ie 20 Hz) resulted in activation of more brain regions than the lower frequency of 5 Hz (Lomarev *et al*, 2002). Dose–response studies of other stimulation parameters will undoubtedly provide additional information to optimize VNS therapy.

There are many other priority items on the clinical research agenda for treatment-resistant depression. Predictors of response to VNS therapy and other strategies for treatment-refractory depression would represent a significant advance in clinical care. Clues from the relatively few clinical studies have provided some promising leads, such as an association between the changes in the ratio of CSF HVA : 5-HIAA concentrations during VNS therapy (Carpenter *et al*, 2004) and PET changes in ventral brain regions (Hagen *et al*, 2003).

Conclusions

VNS therapy appears to be a valuable addition to existing treatments for patients with pharmacoresistant epilepsy. The available data, taken together, suggests that VNS therapy also is a promising and well-tolerated intervention that is effective in a subset of patients with treatment-resistant depression. Evidence from clinical trials of VNS therapy in treatment-resistant depression is growing. As data accumulate, the role of VNS therapy in the depression treatment armamentarium will be better defined. A thorough understanding of the efficacy of new treatments is never completely clear when they are first approved, and VNS therapy is no exception. Dosing trials of VNS therapy in treatment-resistant depression are ongoing, and the findings of these studies in conjunction with the cumulative experience by clinicians will inform future therapeutic choices.

In addition to representing a novel therapeutic modality, VNS therapy is a research tool that offers the hope of better understanding and potentially treating a variety of brain diseases. At the current time, the mechanisms underlying its efficacy for treatment-resistant depression remain incompletely understood. One appealing explanation is that the effects of chronic VNS therapy are mediated by the known direct and secondary projections of the vagus nerve to brain regions involved in the regulation of mood. More specifically, the effects of VNS therapy on noradrenergic neurons in the locus ceruleus and serotonergic neurons in the raphe nucleus are one likely mechanism of action. Rosenbaum and Heninger (2000) speculated that the latency of response in patients with epilepsy or treatment-resistant depression suggests that VNS therapy may trigger a process of neural adaptation rather than directly targeting the specific pathophysiological deficits of the disorder. The results of ongoing, hypothesis-driven clinical and imaging studies will be pivotal to increasing our understanding of the mechanisms of action of VNS therapy of treatment-resistant depression.

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