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Cervical vagus nerve stimulation for treatment-resistant depression

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Intermittent electric stimulation of cranial nerve X (called the "vagus," Latin for "wandering") via a surgically implanted programmable prosthesis was approved by the US Food and Drug Administration (FDA) for medically refractory partial-onset seizures in 1997. Only 4 years later, and without the benefit of controlled data to establish its efficacy, the VNS Therapy system (Cyberonics, Houston, TX) for delivery of cervical vagus nerve stimulation (VNS) had become an approved treatment for medication-resistant or -intolerant depression or bipolar disorder in Europe and Canada. That VNS has come to be regarded as one of the most promising new forms of therapeutic brain stimulation reflects a tremendous need for better long-term treatments of disabling depression as well as great expectations for the application of new technologies in treating mental illness. The history of its development and practical considerations for its application in psychiatric disorders are reviewed in this article.

Anatomy of the vagus nerve

The vagus nerve, best known for its parasympathetic efferent functions, such as autonomic control and regulation of heart and gut viscera, is actually a mixed sensory and motor nerve. Approximately 80% of the vagus is sensory afferent fibers, carrying information to the brain from the head, neck, thorax, and abdomen [1]. Through sensory afferent connections in the nucleus tractus solitarius (NTS), the vagus has extensive projections to brain regions that are thought to modulate activity in the limbic system and higher cortex [2–4]. Pathways connecting the NTS with the parabrachial nucleus and the locus ceruleus (LC) carry afferent vagal input to norepinephrine-containing neurons, which reach the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic structures [5].

Preclinical investigations of vagus nerve stimulation

The first published report suggesting that VNS directly affected central function appeared in 1938, when Bailey and Bremner [2] described synchronized activity of the orbital cortex produced by VNS in cats. Slow-wave response in the anterior rhinal sulcus and amygdala to VNS was noted in awake cats with high cervical spinal section [3]. Further evidence of VNS effects on the basal limbic structures, thalamus, and cingulate was generated by a study in monkeys [4]. A synthesis of this preclinical literature led Zabara [6, 7] to hypothesize and further investigate in dogs the notion that VNS would have anticonvulsant action. Zabara observed VNS-induced cortical electroencephalographic (EEG) changes and seizure cessation in dogs, leading him to postulate

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that the antiepileptic mechanisms of action of VNS would involve direct termination of an ongoing seizure as well as seizure prevention [8]. In preclinical investigations, access to the vagus was achieved through an abdominal or diaphragmatic approach.

Clinical trials of vagus nerve stimulation for epilepsy

In 1988, the first human implants were performed for a pilot study of cervical VNS in patients with medication-resistant epilepsy who were not candidates for neurosurgery [9]. The VNS Therapy system commercially manufactured by Cyberonics includes a pocket watch-sized generator that is implanted subcutaneously in the left chest wall in a fashion similar to placement of a cardiac pacemaker [10]. Bipolar electrode coils are wrapped around the left vagus nerve near the carotid artery in a separate neck incision (Fig. 1). The leads are subsequently tunneled under the skin for connection with the programmable generator. A telemetric wand connected to a portable computer is held to the chest (over the patient's clothing) to assess and control the stimulation parameters in a noninvasive office procedure.

By 1990, the first multicenter pivotal VNS trial was being conducted in the United States and Europe to investigate its role in medically refractory epilepsy [11]. Results from three open trials and two double-blind studies [11,12] indicated a 25% to 30% mean decline in seizure frequency and suggested a tendency for anticonvulsant benefits to be sustained or improved over time with continuing VNS [13,14]. Collective data from the epilepsy trials showed that after 2 years of continuous VNS, the categorical response rate (defined as a 50% or greater reduction in seizure frequency) reached 43% and was maintained at the 3-year mark [13]. Although few epilepsy patients receiving VNS have achieved full remission and become free of anticonvulsant medications, data from these studies supported the use of cervical VNS as a safe and effective adjunct treatment for difficult-to-treat epilepsy [15]. Perhaps more important to the future development of clinical VNS applications, the epilepsy studies demonstrated that cervical VNS was well tolerated, with adverse events (AEs) rarely leading to discontinuation of VNS therapy [16]. Pooled data from epilepsy clinical studies (n = 454) show minimal surgical complications associated with implantation: infection without explantation of the device (1.8%), infection with subsequent explantation (1.1%), hoarseness or temporary vocal cord paralysis (0.7%), and hypesthesia or lower left facial paresis (0.7%) [17]. Side effects related to the intermittent stimulation itself (ie, voice alteration or hoarseness, cough, paresthesia, dyspepsia) were judged to be mild or moderate most of the time and were noted to decrease over time with ongoing VNS at the same "dosage." Stimulation-related AEs could be diminished by reprogramming the device to deliver a lower level of output current. Alternatively, a patient can completely abort a stimulation-induced AE by holding or taping a small magnet over the pulse generator. High continuation rates (72% at 3 years), lack of compliance issues or drug-interactions, and favorable practice and reimbursement economics have all contributed to the success of VNS in the treatment of patients with severe epilepsy. At the time of this publication, more than 20,000 epilepsy patients worldwide have received cervical VNS (S. Perkins, Cyberonics, personal communication 2003), and the treatment has been judged by the American Academy of Neurology's Technology and Therapeutics Committee as having "sufficient evidence . . . to rank VNS for epilepsy as effective and safe, based on a preponderance of Class I evidence" [15].

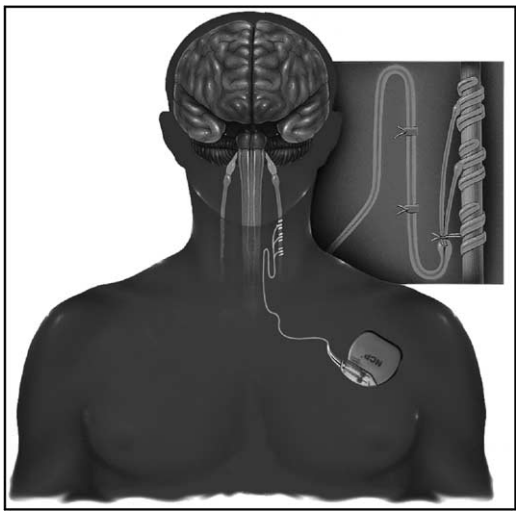

Fig. 1. Schematic representation of placement of the NeuroCybernetic Prosthesis manufactured by Cyberonics, Inc. for therapeutic left cervical vagus nerve stimulation.

Anticonvulsant mechanism of action research

Ascending projections from the NTS to the midline raphe and LC are hypothesized to be the pathways through which VNS exerts antiseizure and neuropsychiatric effects. Studies in rats during VNS reveal increases in cellular activity as measured through the oncogene C-fos in the amygdala, cingulate, LC, and hypothalamus [18]. Further support for a role of noradrenergic neurotransmission comes from a report of suppression of the antiseizure effects of VNS in animals after lesions of the LC [19]. Although the basic mechanisms of action are unknown, a theoretic VNS-induced increase in NTS concentration of γ-aminobutyric acid (GABA) and/or a decrease in NTS glutamate level could explain the antiseizure activity of VNS [20]. Consistent with this hypothesis, a study of lumbar cerebrospinal fluid (CSF) components in epilepsy patients sampled before and after 3 months of VNS showed significant increases in CSF concentrations of GABA and trend-level decreases in glutamate [21]. Other provocative findings from the CSF study were trends toward VNS-induced increases in levels of the major metabolite of dopamine, homovanillic acid (HVA), and the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). A positron emission tomography (PET) study in epilepsy patients demonstrated significant VNS-induced modulation of blood flow in key brain structures thought to be involved in seizures and emotion regulation [22]. Blood flow increases were seen in the rostral medulla, thalamus, hypothalamus, insula, and postcentral gyrus, all with greater activation on the right side. Bilateral decreases were seen in the hippocampus, amygdala, and cingulate gyrus.

Vagus nerve stimulation as a potential treatment for depression

During the early epilepsy trials of VNS, patients frequently stayed in the same hotel in Gainesville, Florida, during follow-up visits at the study site. An astute observation made by a hotel clerk and reported to VNS investigator B.J. Wilder was that the VNS patients seemed to be in better spirits as time passed. Anecdotal reports of mood improvements apparently unrelated to reduction in seizure frequency further inspired the VNS investigators to systematically assess mood and anxiety symptoms [11,12]. Both retrospective data analysis [23] and prospective assessments during epilepsy trials [24] suggested that VNS was associated with a reduction in depressive symptoms, even in the absence of improvement in seizures.

Incidental findings of psychiatric improvements during clinical trials of anticonvulsant therapies have provided the rationale for further investigation into the potential utility of other drugs like carbamazepine in the management of bipolar disorder [25]. In light of the growing number of modern anticonvulsant agents (eg, carbamazepine, valproic acid, lamotrigine) that have demonstrated beneficial effects in mood-disordered patients, a possible role for VNS in the treatment of depression seemed worthy of investigation. The similarities between VNS and electroconvulsive therapy (ECT), considered to be the most effective available antidepressant treatment, also supported the hypothesis that VNS may have primary antidepressant properties. These considerations, together with the known anatomic projections of the vagus to regions of the brain involved in mood regulation and the preclinical and human CSF data suggesting that VNS altered major neurotransmitter systems implicated in depression, provided a rationale for studying VNS in a new population of subjects.

Open-label study of vagus nerve stimulation for treatment-resistant depression (D-01)

The safety and efficacy of VNS for nonpsychotic, chronic, or recurrent treatment-resistant depression was first studied in an open-label fashion in 30 patients at four academic sites in the United States [26]. Patients enrolled in the study, called "D-01," had either bipolar or unipolar forms of affective illness and continued to be severely symptomatic despite exposure to an average of 16 different clinically administered treatments (including an average of five strictly defined adequate antidepressant trials) for the current major depressive episode. The majority (66%) had undergone a course of ECT for the index depressive episode before enrolling in the VNS study and undergoing surgical implantation of the VNS Therapy system. After a 2-week single-blind period for recovery from surgery, the patients began active VNS with an initial 2-week period of stimulation adjustment (consistently programmed to take place in cycles of 30 seconds "on" and 5 minutes "off" but variable in intensity of output current) and a subsequent 8-week

period of fixed-dose VNS. All patients continued on stable psychotropic medication regimens. The categoric response rate (50% or greater decrease in total score on the 28-item Hamilton Rating Scale for Depression [HRSD]) after 10 weeks of adjunctive VNS was 40% for the first 30 patients. Substantial functional improvement was also seen, suggesting acute antidepressant efficacy in a difficult-to-treat depressed population. A second cohort of 30 patients with treatment-resistant depression meeting similar inclusion and exclusion criteria was added to the open-label study. A somewhat less robust response rate of 21% was seen at the end of the "acute phase" (10 weeks of active VNS) for this second cohort. The overall acute response of 30.5% for the combined cohorts (n = 60), with 15% meeting criteria for full remission of the depressive episode, was still much higher than what might be expected in such a severely ill and treatment-resistant population, however.

Quality of life assessments suggested that VNS was associated with improvements in vitality, social function, and mental health domains even among patients who were considered VNS acute-phase nonresponders [27]. Safety data from the D-01 open-label depression study mirrored that of the epilepsy trials, as most side effects were experienced only during stimulation and were considered mild. No dose-response relationship was detected when final output current data were examined. Neuropsychologic tests indicated neurocognitive improvements after VNS relative to baseline, especially in those who experienced decreased depressive symptoms [27]. The only identifiable predictor of response was degree of treatment resistance as measured by the number of failed antidepressant trials in the index depressive episode. More severely refractory patients experienced poorer responses to the 10-week VNS therapy.

Longer term follow-up results: open-label study of vagus nerve stimulation for depression (D-01)

Although the short-term results were considered encouraging, the longer term data generated even more enthusiasm for VNS in treatment-resistant depression. After 1 year of VNS, 91% (10/11) of the first cohort of acute-phase study responders had maintained their response and 18% (3/17) of the initial nonresponders had achieved a reduction of depressive symptoms sufficient to meet "responder" criteria [28]. When the entire sample (n = 59) participating in the open-label (D-01) study was followed to the 1-year mark, the response rate was 45% and the remission rate was 27%. For those who had reached the 2-year mark, there continued to be evidence of sustained or even enhanced response to VNS (13/24 responders [54%]) [29]. It is worth noting that changes in dose or type of psychotropic medication and VNS stimulation parameters were not controlled after exit from the acute-phase study, introducing the possibility that the observed improvements were not entirely attributable to the ongoing VNS. Nevertheless, the association of adjunct VNS with sustained depressive symptom reduction and improved functional status after 2 years is suggestive of antidepressant efficacy in a naturalistic setting.

Pivotal, placebo-controlled study of vagus nerve stimulation for depression (D-02)

Encouraging results from the open-label studies clearly indicated a need for a placebo-controlled investigation of the antidepressant efficacy of VNS. A large-scale pivotal study was thus designed to be almost identical to the open-label study that preceded it, with the exception of double-blind randomization to either active VNS or a sham condition. Additionally, the protocol exclusion criteria were revised to exclude those with the highest levels of treatment resistance (six or more failed adequate trials in the index depressive episode), because they did not appear to benefit from VNS in the open-label study. After completing the 12-week acute study, patients in the sham condition who continued depressed would cross over to active stimulation, and long-term data would be collected on all patients.

Results of the randomized controlled study, called "D-02," were released to the press in early 2002. Two hundred twenty-five patients received VNS (2 weeks of VNS stimulation parameter adjustments and 8 weeks of fixed-dose VNS) in an "add-on" study design. Acute safety and tolerability of VNS were demonstrated. The placebo (sham) response rate was low at 10%, but only 15% responded to active VNS, which failed to confirm the short-term antidepressant efficacy of the adjunct therapy statistically [30].

Speculation about why the D-02 treatment group response was inconsistent with the open-label study results included hypotheses about inadequate dosing of VNS stimulation. A preliminary comparison of the output current

delivered in the D-02 depression study with that used in the initial open-label depression study and in epilepsy studies suggests that stimulation set at 1.0 mA or higher is associated with higher rates of clinical response. Stimulation parameters were at lower settings in the D-02 study compared with those used in the initial open-label D-01 depression studies and epilepsy trials. At present, systematic efforts are underway to "ramp up" or increase the dose of VNS in pivotal study patients who have not yet remitted in hopes of generating data that will better address the possibility of a dose-response relationship for VNS in depression.

Longer term results in the pivotal study (D-02)

In light of the apparent gradual accumulation of more VNS responders over time in the D-01 open-label study, there has been considerable interest in the clinical course and longer term outcomes experienced by the depressed patients who continue to receive VNS after finishing the acute-phase trial. In a preliminary look at data from the first 36 patients to have completed a full year of VNS in the D-02 pivotal study [30], the response rate at the 1-year mark was 44%, which is consistent with 1-year outcomes measured from subjects in the open-label study. Although this finding raises the provocative possibility that VNS simply takes longer (ie, longer than the 10 weeks of acute-phase therapy) to exert its antidepressant effects, the longer term data do not reflect response under continued controlled conditions. It is possible that changes in antidepressant therapies or VNS stimulation parameters account for the growing percentage of patients meeting categorical criteria for antidepressant response over time. More extensive evaluation of follow-up data, with larger sample sizes and over longer periods of exposure to VNS, will eventually be available. Nevertheless, it will remain difficult, if not impossible, to parse out the effects of antidepressant medications or spontaneous remissions in this large cohort and to demonstrate antidepressant effects that can be clearly attributed to adjunct VNS.

Interestingly, recent device regulatory precedents suggest that statistically significant long-term longitudinal results may be appropriate to support FDA approval, particularly in light of the pressing need for safe, tolerable, and effective maintenance treatments for patients with severe chronic and/or recurrent depressions. In summary, it seems premature to conclude either that more placebo-controlled trials of VNS will be needed or that the present data set will be adequate to demonstrate an adequate level of antidepressant efficacy.

"Mechanisms of action" research in depression

One of the most compelling aspects of the VNS development "story" is the growing body of clinical neurobiologic research findings that speak to its direct actions on the brain and central nervous system. Because antidepressant action of VNS has yet to be empirically established, it is not appropriate to interpret dynamic brain imaging results and other biologic correlates of VNS in depressed patients as evidence of its mechanism of antidepressant action. That qualification notwithstanding, such data seem to provide converging lines of evidence that VNS exerts measurable effects in brain regions and neurotransmitter systems implicated in mood disorders.

A single-photon emission computerized tomography (SPECT) imaging study conducted in six depressed patients receiving VNS in the open-label study found that compared with normal controls, patients had reduced regional cerebral blood flow (rCBF) to left dorsolateral prefrontal, anterolateral temporal, and perisylvian temporal structures, including the posterior insula, at baseline [31]. After 10 weeks of VNS, these depressed patients showed increased rCBF in the superior frontal gyrus and right mesial (posterior hippocampus) and lateral temporal cortex. The 10-week trial of VNS seemed to produce resolution of classic rCBF abnormalities in depressed patients, especially among those showing a favorable clinical response.

A method for synchronized blood oxygenation level-dependent (BOLD) functional MRI (fMRI) was developed to detect signal from the implanted device and link it to fMRI image acquisition [32]. In depressed patients, a BOLD fMRI response to VNS was shown in areas regulated by the vagus nerve: orbitofrontal and parieto-occipital cortex bilaterally, left temporal cortex, hypothalamus, and left amygdala. This newly developed fMRI technique was also used to examine whether BOLD signal changes depend on the frequency of VNS [33]. Results confirmed that acute immediate regional brain activity changes vary with the frequency or total dose of stimulation. Additionally, results suggested that VNS exerts a dose-dependent modulatory effect on other brain activities, such as hearing a tone.

Sleep EEG studies have also measured apparent VNS-induced improvement in indices of sleep macro- and microarchitecture in patients with treatment-resistant depression [34]. After 10 weeks of VNS, the amplitude of sleep EEG rhythms was restored to near-normal levels, and patients manifested significantly less awake time and "light sleep" and significantly more stage 2 (deep) sleep.

Lumbar CSF samples were collected in 18 patients both before and after VNS therapy, in the pivotal study (D-02) [35]. Consistent with CSF findings reported for a group of seizure patients receiving 3 months of VNS, the depressed group showed a significant VNS-associated increase in CSF concentrations of HVA, the major dopamine metabolite. Unlike the CSF results obtained during the epilepsy trials, however, no changes in CSF GABA were detected. Although categorical clinical response rates were low, the data suggested that an increase in CSF level of norepinephrine during VNS was correlated with better clinical outcome. This norepinephrine finding is of interest in light of known anatomic connections and animal studies demonstrating that VNS exerts effects on higher brain regions via actions at the LC, the major noradrenergic nucleus in the brain.

Several other types of biologic measures of VNS are currently being investigated to evaluate the effects of VNS in treatment-resistant depression, including evoked response potential (ERP) recordings and provocative neuroendocrine challenge responses. The biologic data thus far suggest that VNS has acute and chronic effects on various key indices of brain activity and neurotransmitter regulation that have also been implicated in mood regulation. As is still the case with most available pharmacotherapies, however, the direct mechanism of therapeutic action of VNS is still not known.

Other potential clinical applications of vagus nerve stimulation

In addition to the use of VNS for treating medication-refractory epilepsy and depression, a number of potential new indications for VNS are being explored. Based on clinical observations from epilepsy and depression studies, results from preclinical and clinical mechanisms of action research, neuroanatomic knowledge, and market opportunities, Cyberonics, Inc. has patents for "application of pulsed electrical signal" in the treatment of movement disorders, eating disorders/obesity, anxiety disorders, dementia and Alzheimer's disease, chronic pain, migraine headache, and cardiac disease. Several of these areas are under current clinical investigation, including an open-label study of bilateral diaphragmatic VNS (using higher output currents than used in cervical VNS applications) for morbid obesity. Multicenter trials of cervical VNS for panic disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and rapid-cycling bipolar disorder are also underway.

Practical considerations in the use of vagus nerve stimulation for psychiatric disorders

Surgical implantation of the VNS Therapy system is considered a procedure of low technical complexity for a surgeon with experience in the head and neck area. The surgery typically takes from 30 minutes to 1 hour in the operating room and is usually performed on an outpatient or day surgery basis, without subsequent admission to the hospital for routine postsurgical recovery or monitoring. General anesthesia is used in most cases, but regional or local anesthesia has been used in some centers. A device "programmer" who is knowledgeable about the operation of the VNS Therapy system must be present but not sterile in the operating room to perform lead testing before surgical incisions are closed. A 4- to 5-cm incision is made in the neck for placement of the two stimulating electrodes, which coil around the vagus nerve (see Fig. 1). A second incision similar in size is made in the chest wall (or alternatively in the axillary region for a superior cosmetic result) for insertion of the pacemaker-like pulse generator. A tunneling tool subcutaneously passes the electrodes to the site connection with the pulse generator. The battery life of the currently available pulse generator model is approximately 8 to 12 years. A single surgical incision is needed in the chest wall to replace the entire pulse generator once the battery has expired.

Because of the potential for heating of the electric leads, whole-body MRI is contraindicated in patients who have the VNS pulse generator implanted. Special "send-receive coils" have been used to concentrate magnetic fields away from the neck area when MRI of the brain is necessary. Patients with the VNS Therapy system are asked

to carry identification cards and are educated about risks related to being in close proximity to strong magnetic fields.

The cost of the VNS Therapy system and surgical implantation for cervical VNS is approximately $20,000, making it to roughly comparable to the cost of a course of ECT for depression in an inpatient setting. If the generator battery life is 10 years, VNS costs can be calculated at about $2000 per year. Early success in establishing adequate terms of coverage and reimbursement by third-party payers has contributed to the wide-scale availability of VNS for patients with epilepsy in the United States. At present, VNS as a treatment for depression remains investigational in the United States; as such, it can be offered only at academic centers conducting approved research protocols. Data regarding the optimal stimulation parameters for antidepressant effects are extremely limited. Because there is much yet to be learned about the effects of various stimulation "doses" and patterns of electric pulse delivery, off-label use of VNS is discouraged at this time. Although it is tempting to imagine that VNS may replace psychotropic medications and the many undesirable side effects that accompany them, it is important to bear in mind that VNS has been investigated as an adjunct therapy rather than as a monotherapy in most cases to date. Patients' expectations for dramatic symptom recovery or even cure from severe psychiatric illness may be fueled by the introduction of new technology and the highly interventional nature of the device implantation surgery. Management of such expectations should be undertaken with great care, particularly in depressed patients, who are at heightened risk for acting impulsively and self-destructively on feelings of disappointment and hopelessness.

With those caveats in mind, it is useful to consider the relation of VNS to other somatic methods of therapeutic brain stimulation, such as ablative neurosurgery, gamma knife neurosurgery, deep brain stimulation (DBS), ECT, MR spectroscopy (MRS), and transcranial magnetic stimulation (TMS). On a spectrum of relative invasiveness of the procedure, with ablative surgery at one end and TMS at the other, VNS might be ranked in the middle [36]. Future applications of VNS may include combining it with brain imaging techniques to evaluate immediate dynamic effects and, possibly, to influence regional focus through adjustment of the stimulation parameters [36].

Summary

Therapeutic brain stimulation through left cervical VNS now has established safety and efficacy as a long-term adjunct treatment for medication-resistant epilepsy. There is considerable evidence from both animal and human studies that the vagus nerve carries afferent signals to limbic and higher cortical brain regions, providing a rationale for its possible role in the treatment of psychiatric disorders. Open-label studies in patients with treatment-resistant depression have produced promising results, especially when response rates at longer term (1 year and 2 years) follow-up time points are considered. Short-term (10 weeks) treatment with VNS failed to demonstrate statistical superiority over sham treatment in a recently completed double-blind study, so antidepressant efficacy has not yet been established. Longer term data on VNS in depressed patients as well as further information regarding the possible dose-response relation will help to determine the place of VNS in the armament of therapeutic modalities available for major depression.

References

[1] Foley JO, Dubois F. Quantitative studies of the vagus nerve in the cat, I: the ratio of sensory and motor studies. J Comp Neurol 1937;67:49–67.
[2] Bailey P, Bremer F. A sensory cortical representation of the vagus nerve. J Neurophysiol 1938;1: 405–12.
[3] Dell P, Olson R. Projections "secondaries" mesencephaliques, diencephaliques et amygdaliennes des afferences viscerales vagales. C R Soc Biol 1951; 145:1088–91.
[4] MacLean PD. Triune brain in evolution: role in paleocerebral functions. New York: Plenum Press; 1990.
[5] Van Bockstaele EJ, Peoples J, Valentino RJ. Anatomic basis for differential regulation of the rostrolateral peri-locus coeruleus region by limbic afferents. Biol Psychiatry 1999;6:1352–63.
[6] Zabara J. Peripheral control of hypersynchronous discharge in epilepsy. Electroencephalogr Clin Neurophysiol 1985a;6(Suppl):S162.
[7] Zabara J. Time course of seizure control to brief, repetitive stimuli [abstract]. Epilepsia 1985;26:518.
[8] Zabara J. Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia 1992;33:1005–12.
[9] Penry JK, Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. Epilepsia 1990; 31(Suppl 2):S40–3.
[10] Amar AP, Heck CN, Levy ML, et al. An institutional experience with cervical vagus nerve

trunk stimulation for medically refractory epilepsy: rationale, technique and outcome. Neurosurgery 1998;43:1265–80.
[11] Ben-Menacham E, Manon-Espaillat R, Ristanovic R, et al. Vagus nerve stimulation for treatment of partial seizures, I: a controlled study of effect on seizures. Epilepsia 1994;35:616–26.
[12] Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation for treatment of partial-onset seizures: a randomized active-control trial. Neurology 1998;51:48–55.
[13] Morris GL, Mueller WM. E01–E05 VNSSG: long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Neurology 1999;53: 1731–5.
[14] Salinsky MC, Uthman BM, Ristanovic RK, et al. Vagus nerve stimulation for the treatment of medically intractable seizures: results of a 1-year open-extension trial. Arch Neurol 1996;53:1176–80.
[15] Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee for the American Academy of Neurology. Neurology 1999;53:666–9.
[16] Schachter SC, Saper CB. Vagus nerve stimulation (progress in epilepsy research). Epilepsia 1998;39: 677–86.
[17] Bruce DA. Surgical complications. Epilepsia 1998; 39(Suppl 6):92–3.
[18] Naritoku DK, Terry WJ, Helfert RH. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. Epilepsy Res 1995;22:53–62.
[19] Krahl SE, Clark KB, Smith DC, et al. Locus coeruleus lesions suppress the seizure attenuating effects of vagus nerve stimulation. Epilepsia 1998; 39:709–14.
[20] Walker BR, Easton A, Gale K. Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. Epilepsia 1999;40:1051–7.
[21] Ben-Menacham E, Hamberger A, Hedner T, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Epilepsy Res 1995;20:221–7.
[22] Henry TR, Bakay RAE, Votaw JR, et al. Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: acute effects at high and low levels of stimulation. Epilepsia 1998;39:983–90.
[23] Scherrmann J, Hoppe C, Kral T, et al. Vagus nerve stimulation: clinical experience in a large patient series. J Clin Neurophysiol 2001;18: 408–14.
[24] Harden CL, Pulver MC, Nikolov B, et al. Effect of vagus nerve stimulation on mood in adult epilepsy patients [abstract]. Neurology 1999;52(Suppl):A238–P03122.
[25] Ballenger JC. Post RM. Carbamazepine (Tegretol) in manic-depressive illness: a new treatment. Am J Psychiatry 1980;137:782–90.
[26] Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: a multicenter study. Biol Psychiatry 2000; 47:276–86.
[27] Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology 2001;25: 713–28.
[28] Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: One year outcomes. Biol Psychiatry 2002;51: 280–7.
[29] Martinez JM, George MS, Rush AJ, et al. Vagus nerve stimulation shows benefits in treatment-resistant depression for up to two years [abstract NR21]. In: APA 2002 Annual Meeting New Research Program. American Psychiatric Association. Washington DC:2002. p. 6.
[30] Marangell LB. Does vagus nerve stimulation change the long term course of mood disorders [abstract 16E]? In: APA 2002 Annual Meeting Syllabus and Proceedings Summary. American Psychiatric Association. Washington DC:2002. p. 263.
[31] Devous MD, Husain M, Harris TS, et al. The effects of VNS on regional cerebral blood flow in depressed subjects. Biol Psychiatry 2002;51(8):152S.
[32] Bohning DE, Lomarev MP, Denslow S, et al. Feasibility of vagus nerve stimulation-synchronized blood oxygenation level-dependent functional MRI. Invest Radiol 2001;36:470–9.
[33] Nahas Z, Lomarev MP, Denslow S, et al. Synchronized BOLD fMRI [abstract]. Biological Psychiatry 2002;51:(8)152S.
[34] Armitage R, Husain R, Hoffman R, et al. The effects of VNS on sleep in depression [abstract]. Biological Psychiatry 2002;51(8)152S.
[35] Carpenter LL, Moreno F, Kling M. The effects of VNS on CSF components in depressed subjects [abstract]. Biological Psychiatry 2002;51(8)152–3S.
[36] George MS, Sackeim HA, Rush AJ, et al. Vagus nerve stimulation: a new tool for brain research and therapy. Biol Psychiatry 2000;47:287–95.