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Vagus Nerve Stimulation: A Proven Therapy for Treatment of Epilepsy Strives to Improve Efficacy and Expand Applications

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***Abstract*—Vagus nerve stimulation (VNS) is an approved therapy for the treatment of adult patients and adolescents aged 12 years and older who have partial onset seizures refractory to antiepileptic medications. More than 50,000 patients worldwide have been implanted with the VNS system. Work continues to understand the mechanism of action of VNS with the goal of improving the treatment, particularly to identify patients who will be helped by VNS, to develop a closed-loop seizure detection system, and to improve the selection of stimulation parameters. VNS has also been approved for treatment–resistant depression, and it may have utility in the treatment of a variety of other medical disorders.**

I. Introduction

THE Cyberonics VNS Therapy™ System, used for vagus nerve stimulation (VNS), received marketing approval from the U.S. Food and Drug Administration (FDA) in July 1997 as an adjunctive treatment for partial onset seizures refractory to antiepileptic medications in adults and adolescents aged at least 12 years. The VNS system consists of an implantable generator, a lead, and an external programming system (including wand, programming software provided on a handheld computer, and a magnet to activate stimulation). Since the time of CE Mark and FDA approvals, >50,000 patients worldwide have been treated with VNS.

Research continues to gain further understanding of VNS and to identify new indications. Increased clinical experience and increased understanding of the mechanism of VNS action has clarified thinking about the utility of VNS; however, questions remain and serve to generate ideas for advancing VNS strategies and technology.

II. Potential Improvements

Because VNS Therapy involves implantation of a pulse generator, electrodes, and a lead, it would be desirable to be able to identify which patients would be likely to respond to the therapy. Unfortunately, medical history has not been shown to be a good predictor of response. An alternative strategy for optimizing patient selection might be an evaluation of external stimulation, specifically transcranial direct current stimulation [1] or trigeminal nerve stimulation [2], [3].

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The VNS System includes magnets that patients or their caregivers can use to stop stimulation, activate an extra train of stimulation in an effort to abort an oncoming seizure, or interrupt a seizure. In a clinical study, patients provided with active magnets reported more success in curtailing seizures than patients provided magnets with stimulation set to zero [4]. Seizure duration appears to be associated with the interval between seizure onset and initiation of stimulation in rats [5]. VNS activation through a closed-loop seizure detection system has been proposed as the next step in VNS technology and was first investigated in nonhuman primates [6].

The most logical approach for detecting seizure activity would be the use of electroencephalograms (EEG) from surface, cortical, or deep brain electrodes. Successful detection of seizure activity has been reported in both surface EEG methods [7] and cortical EEG methods [8]. Deep brain methods are challenging, as these electrodes would need to function reliably for decades. Another potential approach would be detection of sudden changes in heart rate. Increased heart rate has been reported in 87% of patients with seizures and the increase precedes EEG seizure onset by an average of 8 to 14 seconds, depending on seizure type [9].

FDA approval for the VNS System included frequencies up to 145 Hz, ON times up to 4.5 minutes, and outputs up to 12 mA. Cyberonics, however, subsequently elected to restrict the maximum parameters to 30 Hz, ON times to 1 minute, and output to 3.5 mA, primarily based on consideration of battery life and comments from patients that lower frequencies were more comfortable. Although many patients have benefited clinically with this set of therapeutic options, the use of other VNS parameter settings or different patterns of stimulation might improve the effectiveness of VNS for more patients and should be explored. NIH-sponsored studies established safety for ON times up to 4 hours with a 50% duty cycle at 50 Hz, and for continuous stimulation for frequencies of ≤20 Hz [10]. To establish other and possibly more effective parameter-setting strategies, it will be necessary to define the combination of parameters that optimally stimulate the vagus nerve; to identify the factors that enhance signal transmission through the nucleus tractus solitarius; and to determine how the neural networks process the signals for the specific disease states [11].

Some evidence suggests that higher frequencies (i.e., 50 to 143 Hz) have equal, if not greater, effectiveness than a

frequency of 30 Hz [12]. Higher frequencies (e.g., 88 and 143 Hz) may be particularly effective when delivered during a seizure [6]. Delivering a few pulses at a high frequency every few seconds has been shown to facilitate synaptic transfer and optimize the measured evoked potentials in the parafasicular nucleus of nonhuman primates [13].

Lead impedance is another aspect that may affect performance. The circumneural helical electrode is a very energy-efficient design. The electrode encircles the nerve and lightly touches it, thus minimizing the distance from electrode to nerve. The electrode has been shown to be very biocompatible with the delicate nerve structure. Although fibrotic growth does not develop between the electrode and the nerve, the electrode impedance of this design increases to a plateau between 3 and 4 K ohm. The generator has a compliance voltage of 12 V.

Another area of potential research for increased efficacy is that of stimulus delivery, increased duration, and bilateral stimulation. A study in monkeys implanted with a 2-electrode cuff around the right vagus nerve suggested that stimulation at a random frequency of 50-250 Hz is a means to avoid accommodation during periodic stimulation [6].

With regard to increasing the duration of stimulation, most patients are treated with a ≤30-second ON time, but the original clinical study used to obtain FDA approval used a 60-second ON time [12]. A nonclinical study suggested that a 60-minute ON time was more effective than the standard 30 second ON/5 minute OFF in rats [14].

For patients whose seizures occur during certain times of the day or month, increasing stimulation at those times when seizures are known to be more prevalent may be useful. For these patients, stimulation could be reduced or eliminated during times when seizures are less likely or reduced when stimulation interferes with the patient's lifestyle. Additionally, circadian methods may improve effectiveness [15].

The success of bilateral deep brain stimulation for the control of Parkinson's disease suggests that bilateral stimulation of the vagus nerve may improve effectiveness [16], [17]. Although bilateral stimulation is not required because unilateral stimulation produces bilateral effects in the brain [15], the effect of bilateral stimulation might be additive and improve effectiveness. Another advantage of synchronized bilateral stimulation is the possibility of alternating stimulation patterns between the right and left vagus nerves. Nonclinical study results are mixed concerning the advantage of bilateral stimulation, and additional studies are indicated before clinical investigations can be started.

III. Nonclinical progress

Although VNS is administered intermittently, some researchers believe that seizures occurring during the VNS OFF time also are affected [18], but it is unclear whether this 'carry-over effect' occurs only when stimulation is applied during a seizure. In one study, VNS induced slow hyperpolarization in the parietal cortex of the rat that outlasted a 20-second VNS train by 15 seconds [19]. Other researchers have hypothesized that appropriate VNS stimulation during a seizure may have a preventative or antiepileptic effect, which was suggested in a nonhuman primate study [6], [20].

Work continues to understand how VNS affects the cardiorespiratory system. A nonclinical model was developed to correlate VNS with cardiovascular parameters [21]. In another study, VNS was shown to reduce seizure severity and suppress seizure-induced cardiac rhythm changes in rats [22]. BioControl Medical (Yehud, Israel) has completed a study of VNS for congestive heart failure and has obtained CE Mark approval [23].

IV. Clinical progress

A. Epilepsy

VNS received FDA approval >12 years ago, and new clinical research has focused on long-term safety and efficacy of the treatment. Results from a retrospective, multicenter, open-label study in 90 patients showed that the median number of seizures among all patients decreased from 41 seizures/month in the prestimulation period to 15 seizures/month at 5-year follow-up visit [24]. At 1 year, 44% of patients were responders, increasing to 59% and 64% after 2 and 5 years, respectively. Complications and chronic adverse effects occurred in 13% of patients, including 3 with lead breaks due to external injury and 3 with hoarseness, which is a function of output current.

Data from a patient outcome registry showed that patients who had cranial surgery for epilepsy (CS; n = 921) before VNS and patients who had not had surgery (nonCS; n = 3822) before VNS had similar median reductions in seizure frequency (CS: 43%, 43%, 46%, 52%, and 51%; non CS: 47%, 53%, 60%, 63%, and 67%) at 3, 6, 12, 18, and 24 months, respectively [25]. The results of this study suggest that the effectiveness of VNS is maintained during prolonged stimulation, and overall seizure control continues to improve with time.

B. Pediatric Populations

VNS has been studied in the pediatric population and has shown promising results in various cohorts of children with refractory epilepsy. A study of 28 children and adolescents who were treated with VNS using a 6-week rapid ramping protocol had favorable outcomes within 6 months and that was sustained at 24 months [26]. A total of 68% had ≥50% reduction in seizure frequency, including 14% who became seizure-free. Adverse events occurred in 68% of the patients, but most events were transient.

Twenty-four children were enrolled in a study to compare the efficacy of corpus callostomy (n = 14) and VNS (n = 10) [27]. The children were monitored for at least 12 months after treatment, and seizure rates and complications were

evaluated. Of the patients who had a corpus callostomy, 64% had >50% reduction in seizure frequency and 36% had >75% reduction. Of the patients who underwent VNS implantation, 70% had >50% reduction in seizure frequency and 20% had 75% reduction. No significant differences were noted between the 2 procedures in terms of final efficacy. Both treatments were well tolerated with expected side effects only. Whereas implantation of the VNS System is a surgical procedure, it is far less invasive than a corpus callostomy.

Records of 26 children who had VNS with a minimum 18-month follow-up were examined for clinical and seizure characteristics and response to VNS [28]. Fifty-four percent of the children responded to VNS with ≥50% seizure-frequency reduction, and children with Lennox-Gastaut syndrome and tonic seizures had a statistically significantly higher responder rate. Seizure severity, duration, and recovery time decreased, and alertness increased in all responders. The results of these studies and other studies suggest promise for use of VNS for the treatment of epilepsy in the pediatric population.

C. Depression

Patients with chronic and poorly controlled depression need safe, effective, and well-tolerated long-term treatments for their disease. Although many effective treatments are available, not all patients respond adequately [29]. Failure of drug treatment is one of the indications for electroconvulsive and VNS Therapy [30]. VNS produces changes in the activity of medial and prefrontal limbic regions that are associated with regulation of mood [31], and has been shown to be an effective long-term treatment in patients with chronic depression. A long-term clinical trial demonstrated safety and efficacy at 12 months [32]. The FDA approved VNS in 2005 for adjunctive use in adult patients with chronic or recurrent depression for whom at least 4 adequate antidepressant trials had failed to provide adequate relief.

In a European study of 74 patients, VNS appeared to effectively reduce the patients' depression, with increasing efficacy over time [33]. Efficacy ratings were similar to ratings reported from a US study with a similar protocol [34], but at 12 months, patients in the European study had a higher rate of reduction of symptom severity.

V. OTHER POTENTIAL INDICATIONS

As research continues, new indications are studied. These indications have not received marketing approval, but are scientifically interesting.

A. Nonclinical Research

Cytokines, low-molecular-weight proteins, are involved in cell proliferation, differentiation, maturation, and activation of cells in the immune system, both proinflammatory and anti-inflammatory. The vagus nerve has been shown to have rapid and targeted immunomodulatory functions [35]. Research may show how stimulation of the vagus nerve may have utility in treating sepsis, ischemia, and hemorrhagic shock, although stimulation of the vagus nerve for emergencies will require development.

B. Clinical Research - Other Indications

VNS has been investigated in small pilot studies for several other indications:

- Migraine and cluster headaches – In patients with epilepsy, use of VNS has been reported to improve these headaches [36], [37].
- Alzheimer's disease – Patients showed improvement in early months of treatment with VNS, but the effect diminished as their disease progressed [38].
- Multiple sclerosis – VNS was reported to improve cerebellar tremor and dysphagia [39].
- Bulimia – VNS has shown promise in this patient population [40].
- Fibromyalgia – A small study is being sponsored by the US National Institutes of Health to evaluate VNS for treating adults with severe fibromyalgia.
- Essential tremor – Results were statistically but not clinically significant in this setting [41].
- Tourette's syndrome – A report suggests that VNS may be effective [42].
- Anxiety – Modest benefit was noted in this patient population [43].

VI. SUMMARY

VNS has been shown to be a safe and effective treatment over many years in adults and adolescents with epilepsy. More recent work suggests that VNS may be equally safe and effective in pediatric populations. VNS has been approved for treating patients with depression who have not been helped with other treatments. The myriad physiologic actions modulated by the vagus nerve continue to be elucidated and may be exploited for therapy in other disease settings beyond epilepsy and depression.

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