

ASSESSMENT OF VAGUS NERVE STIMULATION FOR EPILEPSY

Report of the Therapeutics and Technology Assessment Subcommittee
of the American Academy of Neurology

Introduction and methodology. Despite a recent surge in availability of new antiepileptic medications and advances in surgical therapy for epilepsy, intractable epilepsy remains a very significant problem. At least 25 to 50% of patients with epilepsy suffer from breakthrough seizures or debilitating side effects of medications. We need a safe and effective treatment for these people, even if it is only palliative. Vagus nerve stimulation (VNS) has been argued to be such a treatment.

This assessment was compiled from literature obtained primarily by search of the Medline database, under the key words phrase “vagus nerve,” and “neurostimulation,” joined by the logical “OR,” and then joined by a logical “AND” with “epilepsy,” for the time period 1966 to 1996. A total of 104 articles were found by this search strategy. Titles and abstracts (where available) were reviewed to select relevant articles. Additional written material, including a compendium of abstracts on VNS (not listed in Medline), was solicited and obtained from Cyberonics. A draft of this review was prepared from the written material, circulated to committee members, and thereby revised. Consensus was reached by written communications and phone conferences among members of the committee.

Animal studies. Cranial nerve X, the vagus nerve, serves as a major source of parasympathetic innervation to the viscera, and a source of fibers to branchiomeric muscles derived from the nucleus ambiguus. According to a recent review by Rutecki,¹ afferents in the vagus nerve connect to the solitary nucleus, medullary reticular formation, area postrema, dorsal nucleus of X, and nucleus cuneatus. From these sites secondary connections proceed to the limbic system, hypothalamus, thalamus, and insular cortex. VNS affects the EEG in a frequency- and intensity-dependent manner.^{2,3} Antiepileptic effects of VNS were first demonstrated by Zanchetti et al.⁴ in a topical strychnine model in cats, and later by Zabara⁵ and other investigators in strychnine and pentylenetetrazol (PTZ)-induced seizures in dogs,⁵ maximal electroshock seizures in rodents,⁶ and pentylenetetrazol seizures in rats.^{7,8}

Mechanisms of VNS effect. The mechanism of the antiepileptic effect of VNS remains uncertain. The spontaneous EEG in people undergoing VNS is not changed to human inspection or frequency domain analysis.⁹⁻¹² Further complicating the issue is the biphasic effect of different parameters of stimulation, which are excitatory in some circumstances and inhibitory in others. Woodbury and Woodbury⁷ suggest that the key is activation of C fibers. This conclusion is challenged by Elam et al.,¹³ on the basis of a complete lack of respiratory and cardiovascular effects in humans treated with VNS. Action of vagus stimulation likely involves

several complex brain systems. Stimulation of the vagus nerve increases *fos* expression in the posterior cortical amygdala, cingulate, retrosplenial cortex, ventromedial and arcuate hypothalamic nuclei, vagus nerve nuclei, locus ceruleus, and the cochlear nucleus.¹⁴

Technique and device. Reid,¹⁵ Penry and Dean,¹⁶ and Landy et al.¹⁷ have described the implantation technique. Left-sided unilateral implantations are safer, since right vagus stimulation produces bradycardia. Surgery can be done under general anesthesia or regional cervical block. The carotid sheath is opened, and two spiral electrodes are wrapped around the vagus and connected to an infraclavicular generator pack. In experienced hands, the procedure is said to take less than 2 hours, and to be well tolerated. The device used in the majority of the initial studies was a programmable stimulator.^{18,19} The stimulation regimen is programmable in advance or patients or family can turn the device on or off at any time by placing a magnet against the subclavicular implant site. This potentially is useful for intercepting seizures with contingent stimulation.

Efficacy. The first stimulator was implanted in November of 1988.²⁰ Early series (EO1 and EO2 studies) comprised 15 patients in an open-label design¹⁶ and in a study by Uthman et al.^{21,22} The mean seizure reduction from the first to last 90-day period was 43.6%.²³ Study EO3 was a blinded, randomized, parallel group study of VNS in treatment of partial seizures, performed at 17 sites in the United States, Canada, and Europe.²⁴ To be eligible, subjects had to be 13- to 60-year-old males or females with simple or complex partial seizures, persisting at six or more per month, despite medical therapy, and had to be free from progressive disease. The mean age of studied patients was 33 years, with seizures for a mean of 21 years. At entry, the mean daily number of seizures was 1.6, reflecting a severely affected cohort. Eligible patients were followed for a 12-week baseline, and a left vagus stimulator was then implanted. Two weeks were allowed for recovery, and subjects were then randomized to a treatment group. A fundamental difficulty with the blinding was the ability of the patients to feel the tingling or hoarseness resulting from turning on the stimulation. The decision therefore was made to randomize patients to a HIGH and a LOW (presumed pseudo-placebo) stimulation group. Stimulation of some type was given to all patients, often individualized within a range. Typical values for the HIGH group were 1.5 mA, 30 Hz, and 0.5-msec pulses, on for 30 seconds and off for 5 minutes. The LOW group received stimulation at 1.25 mA, 1 Hz, and 0.130 msec, on for 30 seconds and off for 90 minutes. Magnet turn-on was active in the HIGH group and inactive in the LOW group. A total of 114 patients were implanted. One patient dropped out because of generator malfunction and three because of protocol violations. The published report²⁴ analyzed the first 67 patients who completed the 14-week acute phase of the trial. Randomization produced comparable groups in terms of age, sex, and seizure frequency. The HIGH stimulation group (n = 31) experienced a mean seizure reduction of 31%, with 39% of patients experiencing 50% or more seizure reduction. The LOW stimulation group (n = 36) showed mean seizure reduction of 11% compared with baseline, with 19% of patients experiencing at least a 50% seizure reduction. This difference was significant at the $p = 0.029$ level, by population t test comparing the mean percentage changes between the groups. In the HIGH group, 21% of seizures were reported to have been aborted by contingent magnet activation, compared with only 9% in the LOW group. Only 26 of 31 patients in the HIGH group and 18 of 36 in the LOW group had secondarily generalized seizures. Differences in secondarily generalized seizure frequencies were not significant.

A follow-up study²⁵ examined the response to stimulation for the 67 patients, all

converted to the HIGH stimulation parameters, for open-label treatment lasting up to 18 months: 44% of patients had more than 50% seizure reduction, which is similar to the initial 39% response. Mean seizure frequency was reduced to 52% of the 12-week baseline. In this group, long-term, five patients discontinued due to lack of efficacy, and one died, no details given. A trend toward continued improvement in the open-label portion of the trial was described.²⁵ This study, however, did not include analysis of those patients who failed to continue VNS during the full follow-up period. A subsequent study was performed at 1 year of all 114 patients implanted in the EO3 study on an intent-to-treat basis.^{26,27} During open-label therapy, seizures were reduced, compared with baseline, by a mean of 20% in months 1 to 3 and 32% in months 10 to 12. When batteries fail, seizure frequency remains better than baseline for about 2 weeks, then deteriorates to baseline frequency.²⁸

Little data is available on VNS in children. Murphy et al.²⁹ implanted vagus nerve stimulators in 12 children with intractable partial, generalized, and mixed types of seizures and followed them for 2 to 14 months. In their open-label design, five of the 12 children had a 90% reduction in seizure frequency.

It would be useful to be able to predict who is likely to have a positive response to VNS. Wernicke et al.³⁰ and Salinsky et al.²⁷ suggested that age less than 34 years, epilepsy of unknown etiology, and early response to VNS were positive predictors of success.

Several measures of VNS efficacy other than seizure frequency can have a role in overall quality of life, but little data is available on such measures for VNS. No clear conclusions can be drawn about seizure duration or intensity from the EO3 study data: major changes were not observed. Global improvement ratings by patients, families, investigators, and blinded interviewers were increased from baseline in both the HIGH and LOW treatment groups, but relative changes were greater in the HIGH group. Cost of the vagus nerve stimulator device and implantation surgery will be several thousand dollars.

Safety. Stimulating electrodes can injure nerves by mechanical trauma, electro-deposition of toxic materials or “excitotoxic” overstimulation.³¹ In general, VNS appears to be a safe procedure. **In the pilot** study on 11 patients,²⁰ 1 patient developed hoarseness and a left vocal cord paralysis, persistent for at least 1 year. Seven patients required electrode repair due to wire fracture. This high frequency of repairs was not encountered in the later studies; as with any new device and surgical technique, there appears to be a learning curve.

Acute side effects in the 114 patients implanted in the EO3 study were reported by Ramsay et al.³² Hoarseness was experienced (at any time during the 3 months) by 38%, throat pain by 13%, coughing by 9%, paresthesias by 5%, and shortness of breath by 5%. Hoarseness, throat pain, and coughing correlated with the stimulus “on” period. Four patients developed superficial wound infections.³³ Only one patient dropped out because of adverse effects. A patient suffered a myocardial infarction during the study, but the relation to VNS is tenuous. One way to measure patient satisfaction with the VNS therapy is to note how many decided to have a second surgery to replace their batteries when needed. According to Mañon-Espaillet,³⁴ 38 of 45 patients (84%) chose battery replacement. VNS was without serious adverse events in the Murphy et al.²⁹ study in children, described above.

In the EO3 study, heart rate beat-to-beat variation is influenced by HIGH parameters of vagus nerve stimulation,³⁵ but the changes are minor and subtle. The clinical significance of this finding is unclear and Kamath et al.³⁵ speculate that the increased parasympathetic tone could be beneficial in some circumstances. Nonetheless, the clinical experience to date with ambulatory ECG monitoring is limited, and the study-group patients have been young (EO3 mean age = 33).

Cardiac arrhythmia has been a theoretical risk with VNS, especially with bilateral or right vagus stimulation.¹⁷ VNS has no effect on gastric acid secretion or gross GI function.³⁶ No clear changes in cognitive functions are seen with VNS.³⁷

A second controlled study of VNS for epilepsy, entitled E05, has very recently been completed. The data on this study are not yet publicly available, but the sponsoring company, Cyberonics, has indicated that the results support conclusions drawn from the E03 earlier randomized clinical trial (statement with permission of Cyberonics). Published details can be expected in the near future.

Conclusions. Vagus nerve stimulation is an interesting and novel therapy for intractable epilepsy. We consider VNS to be promising, but still investigational (Type B), based on some Class I, but mainly Class II and III evidence. The researchers, clinicians, and corporate sponsors are to be commended for approaching this subject with animal research, pilot studies, and then a randomized clinical trial at an early stage. Early work shows that seizures are reduced by VNS in several animal models of epilepsy. Initial pilot trials in 15 patients were encouraging and gave impetus to a randomized prospective trial in 114 patients. This study (designated E03) showed a benefit of HIGH levels of stimulation versus LOW levels of stimulation, with clear statistical significance. Preliminary information on a second controlled clinical trial (E05) suggests that the second trial supports the conclusions from the first trial. VNS is safe. Serious complications, including injuries to the vagus nerve (and theoretically to the carotid sheath), are very rare in the hands of experienced surgeons. Hoarseness, throat pain, and cough are common during stimulation, but not dangerous. The clinical significance of the randomized clinical trial is less clear for the following reasons:

1. No true placebo could be established, since subjects perceived the stimulus. Was the blinding distorted by the patients' ability to distinguish whether they were in the HIGH versus LOW treatment group?
2. The degree of improvement is relatively modest: a mean partial seizure reduction of 31%, with 39% achieving at least a 50% reduction. This rate is comparable to the response rate achieved by several of the new antiepileptic medications.³⁸ Would a patient have surgery for this degree of seizure reduction, where very few experience complete remission of seizures? The answer has to be individualized. Young patients with auras and idiopathic epilepsy have over a 50% responder rate, although these predictors need to be prospectively validated. Some patients sit on the “tail of the curve” and benefit substantially. Improvement may be sustained, or even increased, over time.
3. Trials have not yet demonstrated efficacy of VNS for secondarily generalized seizures, the most debilitating seizures in this population.
4. The mechanism of VNS remains obscure (as of course does the mechanism for several of our “effective” new antiepileptic drugs).
5. Numbers are still small, and experience limited. New drugs are tested on approximately 2,000 to 5,000 people with the target disorder prior to release, and unpleasant surprises sometimes still emerge after release.
6. Vagus stimulator devices and implantation surgery are costly. This modality would be cost-effective only if studies could show decreased doctor and emergency visits, reduced dependence upon antiepileptic drugs, and improved quality of life. Such an outcome analysis remains to be done.

Executive summary. VNS is a new treatment for intractable partial seizures. A stimulator is

placed on the left vagus nerve and connected internally to a programmable pulse generator. Stimuli cycle at regular times or upon demand of a magnet held to the chest at the start of a seizure. Information has been published on about 130 patients undergoing the treatment. During stimulation, the treatment appears to be safe, but subjects may experience hoarseness, cough, and throat discomfort. Pilot studies on 15 patients were encouraging, and a randomized prospective trial of high versus low levels of stimulation (to maintain a partial blind) was successfully completed. Analysis of the first 114 completing patients showed an average partial seizure reduction of 31%, and a 39% responder rate (>50% reduction), with a statistically significant difference between the seizure frequency of patients in the high and the low stimulation groups. Some responders may further improve over time within a period as long as 2 years. The mechanism for the benefit remains uncertain. Given the positive outcome of a controlled trial (and preliminary favorable data on a second controlled trial) and three small uncontrolled trials in adults and children, the good safety of the technique, but the so-far small degree of clinical experience, this panel considers the technique promising in treatment of intractable partial seizures, but not yet established.

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Note. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

DEFINITIONS

Safety: A judgement of the acceptability of risk in a specified situation, e.g., for a given medical problem, by a provider with specified training, at a specified type of facility.

Effectiveness: Producing a desired effect under conditions of actual use.

Established: Accepted as appropriate by the practicing medical community for the given indication in the specified patient population.

Promising: Given current knowledge, this technology appears to be appropriate for the given indication in the specified patient population. As more experience and long-term follow-up are accumulated, this interim rating will change.

Investigational: Evidence insufficient to determine appropriateness, warrants further study. Use of this technology for given indication in the specified patient population should be confined largely to research protocols.

Doubtful: Given current knowledge, this technology appears inappropriate for the given indication in the special patient population. As more experience and long-term follow-up are accumulated, this interim rating will change.

Unacceptable: Regarded by the practicing medical Community EXS as inappropriate for the

given indication in the specified patient population.

Quality of evidence ratings:

Class I: Evidence provided by one or more well-designed randomized, controlled, clinical trials.

Class II: Evidence provided by one or more well-designed clinical studies such as case control, cohort studies, etc.

Class III: Evidence provided by expert opinion, nonrandomized historical controls, or case reports of one or more.

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