Vagal nerve stimulation for the treatment of medically refractory epilepsy: a review of the current literature

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Object. The authors conducted a study to evaluate the published results of vagal nerve stimulation (VNS) for medically refractory seizures according to evidence-based criteria.

Methods. The authors performed a review of available literature published between 1980 and 2010. Inclusion criteria for articles included more than 10 patients evaluated, average follow-up of 1 or more years, inclusion of medically refractory epilepsy, and consistent preoperative surgical evaluation. Articles were divided into 4 classes of evidence according to criteria established by the American Academy of Neurology.

Results. A total of 70 publications were reviewed, of which 20 were selected for review based on inclusion and exclusion criteria. There were 2 articles that provided Class I evidence, 7 that met criteria for Class II evidence, and 11 that provided Class III evidence.

The majority of evidence supports VNS usage in partial epilepsy with a seizure reduction of 50% or more in the majority of cases and freedom from seizure in 6%–27% of patients who responded to stimulation. High stimulation with a gradual increase in VNS stimulation over the first 6 weeks to 3 months postoperatively is well supported by Class I and II data. Predictors of positive response included absence of bilateral interictal epileptiform activity and cortical malformations.

Conclusions. Vagal nerve stimulation is a safe and effective alternative for adult and pediatric populations with epilepsy refractory to medical and other surgical management.

Key Words • vagal nerve stimulator • intractable epilepsy • surgical treatment of epilepsy • medically refractory epilepsy

SEVENTY percent of patients with epilepsy can be treated successfully with 2 or fewer antiepileptic medications, leaving 30% of patients who suffer the additional risk of breakthrough seizures or intolerable side effects of additional medication.7,29 Prior to the availability of VNS, surgical options for refractory epilepsy focused mainly on resective strategies, including anatomical and/or functional temporal lobectomies or lesionectomies.13 These procedures have been proven viable for patients with lesions identifiable on imaging or electrophysiological studies supporting a focal ictus and render 60%–90% seizure free. However, for those patients in whom these criteria are not met, resection has shown equivocal results.5,7

Intermittent stimulation of the left cervical vagus nerve has been shown to reduce the frequency and intensity of seizures, but it has failed to show any visible electroencephalographic changes.16 Putative targets of VNS activity have included multiple thalamic and brainstem sites proposed to desynchronize thalamocortical circuitry involved in seizure propagation.12,16,18,20,21 Zabara30 has demonstrated afferent projections from the vagus nerve, traveling within the nucleus tractus solitarius synapsing in the locus coeruleus and raphe magnus nuclei with effects on the release of norepinephrine and serotonin.

While the mechanism of action of VNS in diminishing the frequency and intensity of seizure activity remains undetermined, multiple clinical investigations have supported its continued use in both the adult and pediatric populations. According to the most recent position statement from the American Academy of Neurology, VNS is indicated for “adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies.”12

We propose, utilizing evidence-based classification and guidelines, to perform a review of the currently available literature on the application of VNS in patients with medically refractory epilepsy.
Methods

An English-language literature search on the use of VNS for the treatment of medically refractory epilepsy was performed utilizing Medline/PubMed search strings including “vagal nerve stimulation,” “epilepsy,” “outcome,” and “efficacy.” This search was further limited to articles regarding humans that were published between 1980 and 2011. To complete the final list of publications for review, a search of relevant references from each of the resulting articles was performed. This group was then examined for inclusion or exclusion in the final analysis based on the following criteria: more than 10 patients evaluated, average follow-up of 1 or more years, inclusion of medically refractory epilepsy, and consistent preoperative surgical evaluation (Table 1).

Each article was classified as providing Class I, Class II, Class III, or Class IV evidence according to the criteria of the American Academy of Neurology. Class I evidence was characterized as a prospective clinical RCT with masked outcome assessment in a representative population; Class II evidence was defined as a prospective matched-group cohort study in a representative population with masked outcome assessment; Class III evidence was defined as all other controlled trials in which outcome assessment was independent of patient treatment; and Class IV evidence was defined as all uncontrolled trials including case reports.

Results

A Medline search and review of reference lists yielded 70 articles meeting search-string criteria. After applying inclusion and exclusion criteria, 20 articles were included in the final investigation: 15 studies focused primarily on an adult population and 5 focused exclusively on a pediatric population. Two studies5,17 met criteria for Class I evidence, 7 as Class II evidence, and 11 as Class III evidence. The mean number of cases investigated per study was 90.7 (range 16–436 cases) with a median of 62 patients. The mean minimum postoperative follow-up was 10.5 months (range 3–24 months).

The majority of publications reported outcome in terms of the frequency of seizure reduction with the majority segregating cases into those with a 50% or greater reduction versus those with less than a 50% reduction. There were 14 publications that used this standard, and of the 1378 patients studied, a mean of 50.9% (range 18.4%–67%) showed a 50% or greater decrease in seizure frequency.1,2,4,5,8–11,15,24–28 Five of the remaining studies used the mean or median frequency reduction from baseline.3,14,17,22,23 The mean seizure reduction in these investigations was 42.8% (range 28%–66%). Four studies additionally included data on the percentage of patients achieving freedom from seizures, typically quoted at the 1-year time frame.9,15,19,28 Of these studies, seizure freedom was reported at a mean of 14.0% (range 9%–27%).

<table>
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<th>Authors &amp; Year</th>
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<th>No. of Patients</th>
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* FU = follow-up; — = not reported.
† Value reflects the intent-to-treat population.
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Class I Evidence

There were 2 RCTs investigating the efficacy of VNS in reducing seizure activity in medically refractory epilepsy. In 1994, Ben-Menachem et al. evaluated 67 patients with intractable seizures in a multicenter, randomized, parallel, double-blind study identified as E03. After a 12-week baseline recording of seizure frequency, patients were randomized to either a high- or low-stimulation 14-week VNS treatment. Plasma antiepileptic drug concentrations were maintained throughout the study. Thirty-one patients receiving high-stimulation VNS experienced a mean seizure frequency percentage reduction of 30.9%, whereas 36 patients receiving low-stimulation VNS had mean seizure reduction of 11.3%. These values were found to be statistically significant.

In 1998, Handforth et al. evaluated 254 patients, 13–60 years of age, with intractable partial seizures in a multicenter, double-blind, randomized, active-control study identified as E05. The patients were required to have at least 6 complex partial, visible partial motor, or secondarily generalized seizures in the month prior to entry. After a 12- to 16-week baseline recording, patients were randomly assigned to a high- or low-stimulation group. The 94 patients receiving high stimulation had a mean reduction in seizure frequency of 28%, whereas the 102 patients receiving low stimulation had a 15% reduction. No significant difference was found between the 2 groups in terms of individuals experiencing a 50% or greater reduction in seizure frequency; however, those experiencing a 75% or greater reduction were statistically more likely to be in the high-stimulation group.

Class II Evidence

The 7 studies meeting criteria for Class II evidence were all prospective cohort investigations designed to assess outcome in long-term follow-up of VNS patients. George and colleagues prospectively followed 67 of the patients initially randomized in the E03 study for an additional 16–18 months. The population included 31 patients initially receiving high stimulation and 36 receiving low stimulation. During this investigation, all patients now received high stimulation. Both groups showed a significant decrease in seizure frequency compared with baseline. The patients initially randomized to the high-stimulation group had a 52.0% mean seizure frequency reduction, whereas those in the low-stimulation group had a reduction of 38.1% compared with baseline. Salinsky and associates performed a similar open-label extension of an RCT in which 100 patients showed significant reductions in seizure frequency with 1 year of prospective follow-up.

Ardesch et al. prospectively evaluated 19 patients with medically refractory epilepsy for a period of 2–6 years (mean 4 years). Their results show a gradual but significant reduction in seizures over the 6 years of study with an approximately 50% reduction in seizure frequency after 5 years. They additionally found a positive effect on seizure severity, seizure duration, and postictal period.

Ben-Menachem and coworkers also found positive results in the long-term follow-up of 64 patients with various refractory epileptic disorders. They reported a 50% or greater seizure reduction in patients with partial seizures, idiopathic generalized seizures, and Lennox-Gastaut syndrome with treatment up to 5 years. Overall, 44% of the patients showed response to treatment.

Class III Evidence

Eleven studies met criteria for inclusion as Class III data, including all 5 of the studies in an exclusively pediatric population. All studies were classified as retrospective reviews with population sizes ranging from 29 to 436 patients (mean 102 patients). Eight of these investigations used the 50% or greater seizure reduction standard and reported a mean of 55.5% (range 38%–64.8%) responding at this level. Three articles reported on freedom from seizures at 1 year with a mean of 9.6% (range 6.9%–13%). The mean minimum follow-up in this group of studies was 11.2 months (range 3–24 months).

The largest study of the group, by Elliott et al., reviewed a single-surgeon experience with a mixed adult/pediatric population with up to 11 years of follow-up. They demonstrated significant reduction in seizure episodes with 90% or greater achieved in 22.5%, 75% or greater in 40.5%, 50% or greater in 63.75%, and less than 50% improvement in 36.25%. On multivariate analysis, focal, eloquent epilepsy was found to be a positive predictor of successful seizure control, whereas the presence of an underlying neuronal migration disorder was found to be a negative predictor.

Two other studies attempted to identify predictors of success by utilizing univariate and multivariate analysis. Ghaemi et al. retrospectively reviewed 144 patients and a minimum of 2 years of follow-up data. They demonstrated seizure freedom in 6.9% and a 50% or greater seizure reduction in 61.8%. On multivariate analysis, 3 factors were found to independently correlate with successful VNS treatment: age at implantation, cortical dysgenesis, and unilateral interictal epileptiform discharges. Janszky et al. similarly presented data obtained in 47 consecutive patients with a minimum of 1 year of follow-up. They were able to demonstrate a 13% rate of seizure freedom, with 2 variables found to significantly predict this freedom. In univariate analysis, these included the absence of bilateral interictal epileptiform discharges and the presence of malformations of cortical development. Following logistic regression analysis, only the absence of bilateral interictal epileptiform discharges was found to correlate independently (p < 0.01).

In the 2 largest pediatric investigations, Elliott et al. and Murphy et al. studied 141 and 96 children, respectively. Both demonstrated a significant number of responders (≥ 50% seizure reduction) with 64.8% and 45%, respectively; however, Elliott et al., having greater statistical power, were able to demonstrate significance at p < 0.0001 in mean reduction of episodes at 38.9%. This investigation was also able to demonstrate a 41.4% rate of 75% or greater seizure reduction. Both studies also investigated possible differences in response among younger (< 12 years of age) and older (12–18 years of age) children and found no statistically reliable results. Murphy et al. also demonstrated no difference in response among long-term epileptics (> 7 years) and those with more recent onset.
Discussion

Building on the work of Bailey and Bremmer in the 1930s and Dell, Olsen, and Zanchetti in the 1950s, Dr. Jacob Zabara formulated a technology that now fills a vital role in the active management of patients with intractable epilepsy. By applying intermittent electrical current to the cervical vagus nerve, he proposed to “desynchronize” cerebral cortical activity, thereby attenuating seizure frequency. His work was followed by application in the first humans in 1988, FDA approval in 1997, and over 20 years of prospective study establishing the role of VNS in the modulation of medically refractory epilepsy.

The application of this technology over the succeeding decades has been refined by hundreds of prospective and retrospective investigations. The initial pilot studies of VNS were designed to establish efficacy and safety and succeeded in reducing seizure frequency with minimal side effects of hoarseness and neck tingling. These were followed quickly by 2 landmark RCTs by Ben-Menachem et al.15 and Handforth et al.17 that established the recommended therapeutic dose. Both Class I investigations supported the notion that initiating treatment with high stimulation was far more likely to achieve the goal of reduction in seizure frequency than lower-level stimulation. Both studies also provided the impetus and support for eventual FDA approval of VNS in 1997 for the adjunctive treatment of refractory epilepsy.

Where the Class I studies established potential efficacy and tolerability, the Class II studies have served to demonstrate longevity and consistency in treatment. With extended follow-up durations from 1 to 6 years, the 7 publications identified here provide strong evidence for the use of VNS in multiple epilepsy syndromes over extended periods of treatment. With large, prospectively collected data sets, the investigations of George et al.14 and Salinsky et al.23 have served to confirm the utility of high-stimulation VNS for increased seizure control. Ben-Menachem et al.8 expanded the prospective application of VNS to patients with generalized seizures and Lennox-Gastaut syndrome. Ardesch et al.1 have shown convincing data that VNS not only decreases the frequency of seizures but may also decrease seizure severity, duration, and postictal period time.

Class III studies, derived from retrospective investigations, have been shown to be far more numerous than the previous 2 classes of data, if not as immediately clinically relevant. These 11 publications demonstrate consistently positive results with continued application of VNS to increasingly diverse populations. Of all of the studies reviewed, these represented, by far, the largest data set in terms of cumulative patients evaluated. This volume of information has been used to establish trends in outcome not otherwise evident in investigations with smaller sample sizes. Focal epileptogenic foci and the presence of cortical malformations have been shown to be positive predictors of success with VNS treatment by multiple investigators, including Elliott et al.,10,11 Janszky et al.,19 and Ghaemi et al.,15 but the issue of most appropriate age of implantation appears to remain subject to argument. Ghaemi et al. found younger age at initiation of treatment to be a positive predictor, whereas both Elliott et al. and Murphy et al. found no statistical correlation between younger age and positive outcome.

Conclusions

Vagal nerve stimulation is a safe and effective alternative for adult and pediatric populations with epilepsy refractory to medical and other surgical management.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Guthikonda, Connor, Nixon. Acquisition of data: Connor, Nixon. Analysis and interpretation of data: Connor. Drafting the article: Connor, Nixon. Critically revising the article: Guthikonda. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Guthikonda. Study supervision: Guthikonda.

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