Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: Long-term outcomes and predictors of response

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Abstract

Objective: The goal of this study was to assess the efficacy and safety of vagus nerve stimulation in a consecutive series of adults and children with treatment-resistant epilepsy (TRE).

Methods: In this retrospective review of a prospectively created database of 436 consecutive patients who underwent vagus nerve stimulator implantation for TRE between November 1997 and April 2008, there were 220 (50.5%) females and 216 (49.5%) males ranging in age from 1 to 76 years at the time of implantation (mean: 29.0 ± 16.5). Thirty-three patients (7.6%) in the primary implantation group had inadequate follow-up (<3 months from implantation) and three patients had early device removal because of infection and were excluded from seizure control outcome analyses.

Results: Duration of vagus nerve stimulation treatment varied from 10 days to 11 years (mean: 4.94 years). Mean seizure frequency significantly improved following implantation (mean reduction: 55.8%, P < 0.0001). Seizure control ≥ 90% was achieved in 90 patients (22.5%), ≥ 75% seizure control in 162 patients (40.5%), ≥ 50% improvement in 255 patients (63.75%), and <50% improvement in 145 patients (36.25%). Permanent injury to the vagus nerve occurred in 2.8% of patients.

Conclusion: Vagus nerve stimulation is a safe and effective palliative treatment option for focal and generalized TRE in adults and children. When used in conjunction with a multidisciplinary and multimodality treatment regimen including aggressive antiepileptic drug regimens and epilepsy surgery when appropriate, more than 60% of patients with TRE experienced at least a 50% reduction in seizure burden. Good results were seen in patients with non-U.S. Food and Drug Administration-approved indications. Prospective, randomized trials are needed for patients with generalized epilepsies and for younger children to potentially expand the number of patients who may benefit from this palliative treatment.

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1. Introduction

An estimated 50 million people worldwide are affected by epilepsy, most of whom are successfully treated with single or multidrug regimens [1]. Treatment-resistant epilepsy (TRE) has been reported to occur in 20 to 30% of patients with epilepsy and can be devastating to patients and their families [1]. These effects can be especially profound in children owing to disruption of critical developmental epochs essential to proper intellectual and social maturation.

Nonsurgical treatment options for TRE include the ketogenic diet, complementary or alternative medical therapies, and biofeedback. Surgical treatment options include resective surgery, disconnection procedures, and stimulation procedures. The most widely used and studied neurostimulation procedure is vagus nerve stimulation (VNS; VNS Therapy System; Cyberonics, Inc., Houston, TX, USA), which has been in use since U.S. Food and Drug Administration (USFDA) approval in 1997 for the treatment of intractable partial epilepsy in adults and children over 12 years of age.

Most of the studies reporting on the efficacy of VNS, however, involve a limited number of patients and often have rather short follow-up durations. We report a consecutive series of more than 400 patients with TRE who underwent long-term VNS therapy for refractory epilepsy, analyze the efficacy and safety of VNS therapy, and examine predictors of VNS treatment success.
2. Methods

2.1. Subjects

Between November of 1997 and April of 2008, 507 patients underwent vagus nerve stimulator operations at the NYU Comprehensive Epilepsy Center or Saint Barnabas Medical Center by a single surgeon (W.K.D.). Seventy-one patients were referred for removal or revision of a device placed at an outside center; 436 consecutive patients with TRE underwent primary insertion of a VNS device at our center and are the subjects of this report. At the initial office visit, all patients were prospectively entered into a database that was created for clinical data storage. Data collected included demographic information, surgical history, physical and neurological exams, epilepsy characteristics, mean weekly seizure frequency (obtained from seizure logs kept by caretakers or patient or caretaker report averaged between the last two office visits), treatment history, and imaging findings. This report is a retrospective analysis of this database.

Each patient underwent a presurgical evaluation that included history and physical, electroencephalography (EEG), magnetic resonance imaging (MRI), and, in most cases, video/EEG monitoring and functional imaging studies. The majority of patients were reviewed at a presurgical multidisciplinary conference (MDC) and deemed to be surgical candidates. Selection criteria for the patients who had VNS device insertion included: multifocal or diffuse seizure onset not amenable to surgical resection (250 [57.3%]); persistent or recurrent seizures following intracranial epilepsy surgery (IES; 127 [29.1%]); antiepileptic drug (AED) toxicity or intolerable side effects (5 [1.1%]); medical unfitness for IES (6 [1.4%]); and patient or family preference for conservative measures prior to or in lieu of possible IES (48 [11.0%]).

Focal seizure onsets were deemed to be in eloquent areas if they were in primary sensory or motor gyri, calcarine cortex, or frontal and temporal speech areas. Following institutional review board approval, subjects undergoing VNS procedures were identified from within the database. Missing data were obtained from office and inpatient charts, operative reports, imaging, and electrophysiological studies. Informed consent was waived by the review board.

2.2. Surgical procedure and outcome assessment

The surgical techniques for subcutaneous and subpectoral implantation of the VNS device have been previously described [2]. The majority of patients who underwent implantation were discharged the same day. A small minority of patients had planned inpatient epilepsy monitoring unit admissions for medication adjustment coinciding with their implantation. Since 1999, the stimulator has been turned on the same day. A small minority of patients had planned inpatient epilepsy monitoring sessions. With their implantation. Since 1999, the stimulator has been turned on the same day. A small minority of patients had planned inpatient epilepsy monitoring sessions.

Retrospective chart review was performed to collect follow-up and outcome data. All patients had the opportunity for at least 1 year of VNS therapy duration unless the device was turned off or removed prior to that time. At the time of last available clinical follow-up, the following data were collected: mean weekly seizure frequency (from seizure logs kept by caretakers or patient or caretaker report, calculated as an average of the last 3 months prior to final follow-up or the last two office visits if a longer follow-up visit ensued), complications of VNS therapy, duration of VNS therapy, timing and reason for revisions and removals of VNS devices and all subsequent surgical procedures. A standardized questionnaire that addresses complications and side effects was completed at each follow-up visit at our centers. Although caretakers were queried about the use of the magnet for seizure prevention or termination, its use was at the discretion of the caretaker or patient, usually dependent on the presence of an aura and not systematically reported.

To limit the bias created by nonresponder attrition, we computed follow-up duration using a last visit carried forward (LVCF) analysis in lieu of a declining-n analysis [3]. Telephone interviews were conducted with patients, families, or caretakers to determine most recent seizure frequency and current AED regimen. For patients who could not be reached by phone, follow-up was censored at time of last office visit or inpatient admission. For patients who underwent device removal or had their devices turned off, follow-up was censored at time of VNS therapy termination. Given the demonstration of VNS effect by 3 months from the randomized trials, we considered patients who had VNS therapy for at least 3 months with clinical follow-up data to have adequate follow-up. Patients who did not have follow-up of at least 3 months were deemed to have inadequate follow-up and were excluded from outcome analyses.

Two hundred forty-five patients were included in a study describing our experience with subrectal and subcutaneous VNS generator placement [2] and another report on the efficacy of VNS in 17 patients with tuberous sclerosis complex [4].

We acknowledge that VNS therapy in patients with generalized epilepsies and children ≤12 years of age is an off-label usage not approved by the US FDA.

2.3. Statistical analyses

Averages are expressed as means ± SD and medians. The numbers of pre- and post-VNS AEDs used were not normally distributed (nonparametric), and pre- and postoperative usage was compared via paired-sample Wilcoxon signed ranks testing. Seizure frequency before and after VNS lacked normal distributions when n < 30 per group (as noted in corresponding tables); therefore, the paired-sample Wilcoxon signed ranks test was employed to compare pre- and postoperative values in those cases. For groups with n ≥ 30 with normal distributions, the paired-sample t test was employed to compare pre- and postoperative seizure frequency within subgroups. Percentage seizure reduction was normally distributed when n > 20 and is reported as both median values and mean values with 95% confidence intervals. Uni- and multivariate linear regression analyses were performed to determine the impact of the following independent variables (continuous, dichotomous, or multinomial) on mean percentage seizure reduction (dependent variable): age at epilepsy onset, age ≤ 5 years at onset of epilepsy, age at implantation, age > 12 years at implantation, age > 18 years at implantation, duration of epilepsy prior to VNS, duration of epilepsy > 10 years prior to VNS therapy, prior IES, number of prior IESs, preimplantation seizure frequency, number of reported seizure types, focal seizures only, epilepsy classification and etiology, underlying diagnosis if applicable, EEG findings, number of reimplantation AEDs, number of failed AEDs and history of infantile spasms, febrile seizures, developmental delay, or status epilepticus. Demographic and clinical data comparing patients with and those without adequate follow-up were evaluated with Fisher’s exact test for proportions, The Mann–Whitney U test for nonparametric data, and Student’s t test for parametric data. All variables with a P value of <0.10 on univariate analyses were entered stepwise into the multivariate linear regression model. All statistics were performed using SPSS Version 17.0 for Mac (SPSS Inc., Chicago, IL, USA). A two-tailed P value <0.05 was considered statistically significant.

3. Results

3.1. Patient demographics and clinical data of the primary implant group

Patient demographics and clinical data for the 436 patients (220 females/216 males) who had primary implantations are summarized in Table 1.
A majority of patients (221 [50.7%]) had unknown etiologies for their epilepsy. Among patients with underlying etiologies, the most common causes included cerebral palsy/static encephalopathy (35 [8.0%]), infection (33 [7.6%]), and neuronal migration disorders (33 [7.6%]). Multifocal partial epilepsy was the most common type of epilepsy (174 [39.7%]) followed by idiopathic generalized epilepsy (75 [17.2%]) and symptomatic generalized epilepsy (71 [16.3%]). The most common EEG finding was multifocal activity (199 [45.6%]) followed by diffuse/generalized (158 [36.2%]) and focal (46 [10.6%]) activity.

3.2. Seizure control outcomes and follow-up

The mean duration of VNS therapy was 4.94±3.2 years for the entire cohort (range: 3 months to 11.4 years). Twenty-six domestic patients and 7 patients who returned to foreign countries following implantation had inadequate further follow-up (<3 months following surgery) and were unreachable by phone. Seventeen patients (3.9%) died during the 10-year review period at a mean age of 47±18.6 years (range: 18–79). Five patients died of causes directly related to their seizures (status epilepticus – 3, seizure/drowning – 1, seizure/aspiration pneumonia – 1); the remaining 12 patients died of unrelated causes. Fig. 1 is a flowchart summarizing the follow-up of all patients who had VNS surgery at our centers.

Excluding 33 patients with inadequate follow-up (7.6%) and 3 patients who had devices removed before 3 months because of infection, 400 patients (91.7%) were available for outcome analyses (follow-up >3 months). There were no significant differences between patients with and without adequate follow-up in terms of sex distribution, age at seizure onset, duration of seizures, age at VNS device insertion, seizure types, seizure frequency, EEG findings, or past or present AED usage (P>0.05 for all comparisons). The mean percentage seizure reduction was 55.8% (median: 59.2%, range: 0 to 100%). The median weekly seizure frequency was 1.5, significantly decreased from 4 preoperatively (P<0.0001). There was no significant difference in number of AEDs taken at time of last follow-up when compared with preoperative baseline (3±1.0; P=0.15).

Excluding 33 patients who lacked adequate follow-up, ≥90% seizure control was achieved in 90 patients (22.5%), ≥75% seizure control in 162 patients (40.5%), ≥50% improvement in 255 patients (63.75%) and <50% improvement in 145 patients (36.25%). Forty-nine patients (12.25%) experienced no reduction in seizure burden and 11 patients (2.75%) had an increase in seizure activity from their presurgical baseline. Four of 49 patients (8.2%) who experienced no reduction in seizure burden with chronic, intermittent stimulation experienced some benefit from the use of the magnet in terms of seizure prevention (in cases with aura), termination (most common),

Table 1

Demographic and clinical data for 436 patients who underwent VNS for treatment-resistant epilepsy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) or mean±SD (range)</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>220 (50.5%)</td>
</tr>
<tr>
<td>Males</td>
<td>216 (49.5%)</td>
</tr>
<tr>
<td>Age at seizure onset</td>
<td>9.4±11.5 (birth–59 years)</td>
</tr>
<tr>
<td>Duration of epilepsy prior to VNS</td>
<td>19.2±13.0 (8 months–66 years)</td>
</tr>
<tr>
<td>Age at VNS insertion</td>
<td>250±16.5 (1.3–76)</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>307 (70.4%)</td>
</tr>
<tr>
<td>Children &lt;18 years</td>
<td>129 (29.6%)</td>
</tr>
<tr>
<td>Children ≥12 years (off-label usage)</td>
<td>86 (19.7%)</td>
</tr>
<tr>
<td>Patients &gt;12 years of age</td>
<td>350 (80.3%)</td>
</tr>
<tr>
<td>Median seizure frequency (per week)</td>
<td>4 (0.1–2000)</td>
</tr>
<tr>
<td>Number of AEDs</td>
<td>2.7±1.0 (0–7)</td>
</tr>
<tr>
<td>Number of AEDs failed</td>
<td>5.6±2.8 (1–19)</td>
</tr>
<tr>
<td>Prior failed intracranial epilepsy surgery</td>
<td>127 (29.1%)</td>
</tr>
<tr>
<td>Number of seizure types</td>
<td>2.9±1.0 (1–6)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>221 (56.4%)</td>
</tr>
</tbody>
</table>

Table 2

Seizure control outcomes by modified Engel and McHugh outcome classifications following VNS therapy in 400 patients with complete follow-up.

<table>
<thead>
<tr>
<th>Class</th>
<th>Modified Engel description</th>
<th>No. (%)</th>
<th>McHugh description</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Seizure-free</td>
<td>30 (7.5%)</td>
<td>80–100% reduction in seizure frequency</td>
<td>136 (34.0%)</td>
</tr>
<tr>
<td>II</td>
<td>Rare, nondisabling simple partial seizures</td>
<td>52 (13.0%)</td>
<td>50–79% reduction in seizure frequency</td>
<td>119 (29.8%)</td>
</tr>
<tr>
<td>III</td>
<td>&gt;90% reduction in seizure frequency</td>
<td>173 (43.25%)</td>
<td>&lt;50% reduction in seizure frequency</td>
<td>96 (24.0%)</td>
</tr>
<tr>
<td>IV</td>
<td>Rare complex partial seizures</td>
<td>145 (36.25%)</td>
<td>Magnet benefit only</td>
<td>4 (1.0%)</td>
</tr>
</tbody>
</table>

or improved postictal state. Thirty-three patients (8.25%) have remained seizure free for at least 6 months prior to the last follow-up visit. Table 2 summarizes the seizure control outcomes by modified Engel [5] and McHugh [6] classifications for all patients with adequate follow-up data.

Thirty-five patients (15 females, 16 children) had a total of 41 IESs following VNS device removal at a mean duration of 35.9 months of VNS therapy. The median percentage seizure reduction was 33.3% for this cohort, 24 of whom were Engel Class IV (68.6%). The reasons for
removal were worsening of seizures (2), infection/exposed hardware (1), and inadequate efficacy (32). Twenty-four patients had resections of seizure foci, 5 had callosotomies, 1 underwent hemispherectomy, 9 had electrodes only, and 2 had thalamoscopies. Five patients had their devices replaced immediately following planned palliative cranial surgery (callosotomy, 1) or at the time of electrode removal (electrodes only, 4). Six other patients had their devices replaced in a delayed fashion following IES. These patients experienced a median seizure reduction of 49% following IES (range: 0–100%). Of note, 10 patients who had IES after VNS had been counseled to undergo IES after discussion at MDC, but family preference was VNS. These 10 patients experienced a median decrease in seizure burden of 75.7% and 4 became seizure free.

3.3. Surgical results and complications

The leads were placed on the left vagus nerve in all patients. Generators were placed subpectorally in 259 patients (59.4%) and subcutaneously in 177 patients (40.6%).

The most common side effect was mild but tolerable neck pain associated with the output current, which occurred in 15% of patients. In all but a few cases, this resolved spontaneously over the course of a few weeks or with adjustment of the stimulation parameters.

Complications are summarized in Table 3. Twelve patients (2.8%) experienced varying degrees of permanent vagus nerve injury that included mild but permanent hoarseness in 9 patients (2.3%), dysphagia in 2 patients (0.5%), and unilateral vocal cord paralysis in 1 patient (0.2%). Vocal cord paralysis resolved following device removal. Eleven patients (2.5%) developed significant complications including infection requiring device removal in 7 patients (1.6%); persistent, severe neck pain synchronous with the duty cycle resistant to alteration in parameters and requiring lead revision in 3 patients (0.7%); and pneumothorax in 1 patient (0.2%). There was no difference in the incidence of complications between adults and children or between patients older and those younger than 12 years of age.

3.4. Device revisions and removals

One hundred twenty-nine patients (29.6%) underwent a total of 155 VNS revisions after primary implantation at our center. Generator changes alone were performed in 129 cases, lead revision alone in 1 case, and complete VNS revision (generator and lead) in 25 cases. The most common indication for revision was generator power depletion and occurred at a mean of 47.7±18.9 months following implantation and occurred at a mean of 23–106 months. Lead fracture occurred in 20 devices and presented with delayed neck pain in synchrony with the duty cycle (17) or by loss of device efficacy (3).

Seventy-four patients (17.0%) underwent device removal following primary insertion at our center at a mean of 40.4±30.6 months. Indications for VNS device removal were nonefficacy/worse seizures (32), MRI for possible or planned IES or other MRI indications (31), infection (7), AED success (3), and vocal cord paralysis (1). There were no complications during device removal.

For lead revisions or removals, a very small portion of the helical electrode is left in situ to limit damage to the vagus nerve. The lead is entirely removed in the setting of infection.

3.5. Predictors of seizure control with vagus nerve stimulation therapy

On univariate analysis (Supplemental Table 1—see Appendix), focal EEG findings predicted improved seizure control (n = 46, P = 0.004) and there was a trend for patients exhibiting exclusively focal seizures having better seizure control (P = 0.09). There was no difference in the mean percentage seizure reduction between adults and children (58.2% vs 56.5%, P = 0.66), patients who failed prior IES (58.2% vs 54.9%, P = 0.34), and those who had MDC recommendations for IES over VNS (59.3% vs 56.0%, P = 0.39). No purported markers for more severe epilepsy (duration of epilepsy, number of seizure types, number of failed AEDs) predicted a worse response to VNS therapy.

Table 4 summarizes the mean percentage seizure reduction by epilepsy classification, underlying etiology of epilepsy, and EEG findings following VNS therapy.

Although patients with focal or temporal epilepsy experienced the most robust response to VNS (mean reduction: 74.6%), patients with
multifocal and generalized epilepsies had a significant reduction in seizure burden (mean reduction: 53.8–64.3%). The only exception was in patients with myoclonic epilepsy (n = 7, P = 0.068), but the small numbers of patients in this cohort limit meaningful comparison.

Analysis of the TRE etiology showed that patients with neuronal migration disorders tended to have a poorer response to VNS (mean reduction: 44.5%) compared with patients with other etiologies. However, these patients still experienced a significant reduction in seizure burden (P = 0.02). Patients with traumatic brain injury, cerebral palsy, Lennox–Gastaut syndrome, and infectious etiologies experienced significant reductions in seizure burden (54.3–68.4%) that were not different from the majority of the study group who had unidentifiable TRE causes (mean reduction: 57.0%).

Analysis of the impact of EEG findings on VNS efficacy demonstrated that patients with focal activity (mean reduction: 68.9%) had a more robust response than patients with multifocal activity (56.2%), those with diffuse activity (56.2%), and those with both multifocal and diffuse EEG activity (51.8%). However, there was a significant reduction in seizure burden regardless of EEG activity (P < 0.035 for all groups).

Importantly, worse efficacy was not noted in patients with generalized TRE, an indication for VNS that is not currently approved by the US FDA.

On multivariate analysis, focal epilepsy (eloquent) or TLE (n = 34, P = 0.004) predicted improved seizure control compared with other types, whereas the presence of an underlying neuronal migration disorder predicted a less robust response to therapy (n = 32, P = 0.04) compared with other etiologies. Given the high correlation/colinearity of focal/TLE and focal EEG findings, the latter were not included in the multivariate model.

4. Discussion

In this retrospective review of 436 patients with TRE who underwent VNS device implantations, we report meaningful reduction in seizure burden (≥50%) in more than 60% of patients. Although the most frequently reported side effects were hoarseness and discomfort during the stimulation and ramp-up periods, most of these side effects resolved spontaneously or with alteration of stimulation parameters. Serious complications causing permanent neurological injury or device removal were few (<3%). VNS worked well for all epilepsy types, etiologies, EEG findings, and age groups, including non-US FDA-approved indications such as generalized epilepsies and children aged 12 and under. Clinical characteristics associated with improved response to VNS therapy included focal or temporal epilepsy. Patients with an etiology of neuronal migration disorders tended to respond less well. Purported markers of more severe epilepsy such as duration of seizures, number of seizure types, number of failed AEDs, and failed IES did not portend worse outcomes.

4.1. Efficacy of vagus nerve stimulation

Leading to US FDA approval were two randomized, active-control trials that demonstrated a median reduction in seizure frequency of 25 to 30% at 3 months. Ben Menachem et al. [7] performed a randomized, active-control trial of 67 patients comparing high-stimulation VNS therapy with low-stimulation therapy. They reported a median reduction in seizure frequency of 30.9% in the high-stimulation group compared with 11.3% in the low-stimulation control group after 3 months of therapy. At follow-up, this study was prospectively extended with all patients receiving high stimulation, and follow-up was available for 50 of 67 patients at 18 months postimplantation. The mean reduction in seizure frequency increased to 52% in the original high-stimulation group and to 38% in the original low-stimulation group [8]. Studying 114 patients in a similar active-control trial, George R and colleagues of the Vagus Nerve Stimulation Study Group [9] reported a 24.5% reduction during high stimulation and 6.1% reduction in the control group at 14 weeks following implantation.

In a study of adults and children with partial-onset epilepsy, Handforth et al. [10] randomized 95 patients to receive high- and 103 patients to receive low-stimulation VNS therapy. After 3 months of treatment, they reported a mean reduction in seizure frequency of 28% in the high-stimulation group, compared with 10.6% in the low-stimulation cohort.

Subsequent nonrandomized studies in similar populations and those with off-label indications (children <12 years of age, generalized epilepsies) and more heterogeneous populations have demonstrated nearly 30 to 50% improvement in seizure control [3,11–23]. Most of the published studies, however, are limited by small numbers of patients or relatively short follow-up times. Table 5 summarizes results from the major series of patients with TRE treated with VNS therapy.

Two of the largest series examining the efficacy of VNS for TRE were derived from the Cyberonics registry, a database that gathers clinical data via voluntary participation by patients and their families, a potential source of bias. Amar and colleagues [12] compared the reduction in seizure burden following VNS insertion of 3822 patients without a prior history of IES with that of 921 patients with persistent seizures following cranial surgery. In patients without prior IES, 62% had ≥50% reduction in seizures and 27% had ≥90% reduction in seizure burden. Patients who failed IES had a poorer response to VNS therapy as 55% of patients had ≥50% and 17% had ≥90% reduction in seizure frequency. Using the same registry, Labar [24] examined 1407 patients with a minimum 1-year duration of VNS therapy and follow-up. They reported no difference in VNS efficacy between patients who remained on a stable AED regimen (n = 896, 58% median seizure reduction) and those who required more AEDs or changed medications (n = 511, 55% median seizure reduction).

DeGiorgio and colleagues [17] prospectively observed 195 patients with partial and generalized TRE and reported a median reduction in seizure burden of 40% at a follow-up duration of 12 months. Vonck et al. [23] prospectively examined the efficacy of VNS in 118 adults and children with TRE who received at least 6 months of VNS therapy. At a mean follow-up duration of 33 months, they noted a 55% mean reduction in seizures. Similar results have been noted in adolescents and children under 13 years of age [19,20].

In our study population, nearly 60% of patients experienced a meaningful reduction in seizure burden. Our results (mean seizure reduction of 56%) are higher than those reported in the initial randomized studies (25–30% reduction) but not dissimilar to those of other, nonrandomized studies [11,18,21,24–27]. We believe the greater seizure control in the nonrandomized, postapproval studies is likely secondary to longer duration of therapy that allowed more titration of the stimulation parameters and further AED regimen adjustments over time. The median follow-up for our study was nearly 5 years, markedly longer than the 3-month duration of VNS therapy for the randomized trials. For such nonrandomized, predominantly retrospective studies, however, selection bias, heterogeneity of the patient population, and less systematic determination of seizure frequency cannot be ruled out. We agree with the conclusion of Amar and colleagues [12] that longer-term titration of stimulation parameters and adjustments to the AED regimen may help maximize the effectiveness of VNS therapy over time.

Few predictors of VNS efficacy have been consistently reported in the literature. One of the most common findings reported is improved seizure control with increasing duration of VNS therapy [12,17,19,26,28–30]. We must note the possibility of bias using declining-N analyses which are subject to nonresponder attrition. Others have reported the following variables as predictors of improved response to VNS: older age at VNS insertion [26], younger age at VNS insertion [11], shorter duration of epilepsy [21], longer duration of epilepsy [26], fewer failed AEDs [21], higher baseline seizure frequency [31], prior corpus callosotomy [19,26], higher cognitive...
function at baseline [32], and focal rather than generalized seizures [26]. Reported negative predictors include prior failed IES [12], prior lobectomy [19], and children compared to adults [15].

We noted that patients with focal epilepsy (focal EEG findings, TLE or focal seizures in eloquent cortices) had excellent responses well to VNS therapy, whereas the presence of structural abnormalities secondary to neuronal migration disorders predicted a poorer response. Nevertheless, patients with all types of epilepsies, etiologies, EEG findings, and age groups responded well to VNS therapy. Surprisingly, suspected markers for more severe epilepsy such as developmental delay did not predict a poorer response to VNS therapy.

We have attempted to limit the inaccuracy in treatment outcomes. We have attempted to limit the inaccuracy in this study was performed via retrospective query. Follow-up was not less efficient than VNS efficacy. Determination of seizure frequency and use efficacy of magnetic swiping relied on the report of patients or caretakers and is inherently subject to error. However, this limitation is common to most studies measuring seizure frequency and treatment outcomes. We have attempted to limit the inaccuracy in determining seizure reduction by using LVCF analysis instead of declining-n analysis. The correlation of increased VNS duration with better outcomes reported by some centers may be inherently inaccurate. Ideally, analysis must be performed on the same patients in a serial manner. Patients whose devices do not work often have them removed (nonresponder attrition); and conversely, patients experiencing VNS therapy success tend to continue treatment leading to a biased correlation of increased VNS therapy duration with efficacy. Thus, we chose to use percentage seizure reduction at LVCF instead of declining-n analysis and, similar to Uthman et al. [3], believe our values are more representative of actual VNS efficacy in this population.

4.2. Complications of vagus nerve stimulation

Throat pain, voice changes, and cough during stimulation are the most commonly reported side effects and usually abate with time or alteration of the stimulation parameters [3,11,13,18,29,35]. Significant or permanent injury to the vagus nerve and development of dysphagia following implantation were rare (<0.5% in our series) and comparable to the reported rates (≤4% in most series). Similar to other implantable devices, the rate of infection was under 3% as reported in most large series (0–8%).

Compared with the potential functional deficits from lesionectomy and lobectomy procedures and the risk of disconnection from corpus callosotomy [36], the relative risks of a “minimally invasive” and fully reversible procedure like VNS are minor, often self-limited, and well tolerated by patients. Importantly, the most common adverse effects (cough, voice change, and throat pain during stimulation) are not dangerous to the patient.

4.3. Study limitations

Although patients were entered prospectively into the database, this study was performed via retrospective query. Follow-up was unavailable in 8% of patients, providing a small margin of error in our estimates of VNS efficacy. Determination of seizure frequency and use efficacy of magnetic swiping relied on the report of patients or caretakers and is inherently subject to error. However, this limitation is common to most studies measuring seizure frequency and treatment outcomes. We have attempted to limit the inaccuracy in determining seizure reduction by using LVCF analysis instead of declining-n analysis. The correlation of increased VNS duration with better outcomes reported by some centers may be inherently inaccurate. Ideally, analysis must be performed on the same patients in a serial manner. Patients whose devices do not work often have them removed (nonresponder attrition); and conversely, patients experiencing VNS therapy success tend to continue treatment leading to a biased correlation of increased VNS therapy duration with efficacy. Thus, we chose to use percentage seizure reduction at LVCF instead of declining-n analysis and, similar to Uthman et al. [3], believe our values are more representative of actual VNS efficacy in this population.

A design limitation inherent to all retrospective, nonrandomized studies on VNS is the lack of a control group. Sparse data exist concerning the natural history of seizure severity and frequency in patients with chronic TRE. Direct comparison of pre- and post-VNS seizure frequency, often with an interval of 5 to 10 years in our study, is predicated on the assumption that seizure frequency remains constant over time. Although we cannot confirm this implicit assumption, by definition these patients had TRE and had failed medical treatment for a mean of 19 years prior to VNS implantation. Given such severe epilepsies exhibited by many patients in this cohort and the long history of treatment failures, we are confident that our results are not significantly skewed by a spontaneous decline in seizure frequency over time.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Design</th>
<th>Patient population</th>
<th>Follow-up duration (months)</th>
<th>Mean/median seizure reduction</th>
<th>≥50% Seizure reduction</th>
<th>≥75% Seizure reduction</th>
<th>≥90% Seizure reduction</th>
<th>Seizure freedom</th>
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</thead>
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<tr>
<td>Ben-Menachem et al., 1994 [7]</td>
<td>67</td>
<td>RCT</td>
<td>Both</td>
<td>3.5</td>
<td>30.9%</td>
<td>39%</td>
<td></td>
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</tr>
<tr>
<td>George/VNNSG, 1995 [9]</td>
<td>114</td>
<td>RCT</td>
<td>Both</td>
<td>3.5</td>
<td>24.5%</td>
<td>31%</td>
<td></td>
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</tr>
<tr>
<td>Handforth et al., 1998 [10]</td>
<td>198</td>
<td>RCT</td>
<td>Both</td>
<td>3 38%</td>
<td>23.4%</td>
<td>10.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Giorgio et al., 2003 [16]</td>
<td>64</td>
<td>RCT</td>
<td>Both</td>
<td>3 29%</td>
<td>30%</td>
<td>21%</td>
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</tr>
<tr>
<td>Amar et al., 1999 [13]</td>
<td>164</td>
<td>Prosp Obs</td>
<td>Adults</td>
<td>15 34%/45%</td>
<td>39%</td>
<td>21%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Giorgio et al., 2000 [17]</td>
<td>195</td>
<td>Prosp Obs</td>
<td>Both</td>
<td>12 40%</td>
<td>35%</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vonck et al., 2004 [23]</td>
<td>118</td>
<td>Prosp Obs</td>
<td>Both</td>
<td>33 55%</td>
<td>51%</td>
<td>2.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ben-Menachem et al., 1999 [8]</td>
<td>64</td>
<td>RCT</td>
<td>Both</td>
<td>20 —</td>
<td>40.4%</td>
<td>17%</td>
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</tr>
<tr>
<td>Frost et al., 2001 [18]</td>
<td>50</td>
<td>Retrospective</td>
<td>Both (LGS)</td>
<td>6 58%</td>
<td>56%</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helmers et al., 2001 [19]</td>
<td>125</td>
<td>Retrospective</td>
<td>Children</td>
<td>— 45%</td>
<td>51%b</td>
<td>—</td>
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</tr>
<tr>
<td>Scherrman et al., 2001 [22]</td>
<td>95</td>
<td>Retrospective</td>
<td>Adults</td>
<td>15.8 30%</td>
<td>45%</td>
<td>12%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Murphy et al., 2003 [20]</td>
<td>100</td>
<td>Retrospective</td>
<td>Children</td>
<td>32.4</td>
<td>45%</td>
<td>29%</td>
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<tr>
<td>Uthman et al., 2004 [3]</td>
<td>48</td>
<td>Retrospective</td>
<td>Both</td>
<td>38.4</td>
<td>60%</td>
<td>42%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alexopoulos et al., 2006 [11]</td>
<td>49</td>
<td>Retrospective</td>
<td>Children</td>
<td>24 60%</td>
<td>59%</td>
<td>43.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benifla et al., 2006 [14]</td>
<td>41</td>
<td>Retrospective</td>
<td>Children</td>
<td>31 —</td>
<td>41.5%</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Herdt et al., 2007 [15]</td>
<td>138</td>
<td>Retrospective</td>
<td>Both</td>
<td>44 51%</td>
<td>59%</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amar et al., 2004 [12]</td>
<td>921</td>
<td>Registry</td>
<td>Failed IES</td>
<td>—</td>
<td>55%</td>
<td>31.4%</td>
<td>17.3%</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>3822 Registry</td>
<td>No Prior IES</td>
<td>—</td>
<td>—</td>
<td>62%</td>
<td>43.7%</td>
<td>26.8%</td>
<td>8.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labar et al., 2002 [24]</td>
<td>511</td>
<td>Registry</td>
<td>Change AED</td>
<td>12 55%</td>
<td>56%</td>
<td>33%</td>
<td>19%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>896 Registry</td>
<td>Stable AED</td>
<td>12</td>
<td>58%</td>
<td>57%</td>
<td>37%</td>
<td>21%</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renfroe et al., 2002 [21]</td>
<td>120</td>
<td>Registry</td>
<td>VNS early</td>
<td>3 50%</td>
<td>50.8%</td>
<td>55%</td>
<td>37%</td>
<td>21%</td>
<td>7%</td>
</tr>
<tr>
<td>2785 Registry</td>
<td>VNS later</td>
<td>3</td>
<td>48%</td>
<td>49.6%</td>
<td>28%</td>
<td>14.3%</td>
<td>4.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labar et al., 2004 [26]</td>
<td>260</td>
<td>Registry</td>
<td>Stable AED for 12 months</td>
<td>12 58%</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>436</td>
<td>Retrospective</td>
<td>Both</td>
<td>59.2 55.8%</td>
<td>63.8%</td>
<td>40.5%</td>
<td>22.5%</td>
<td>7.5%</td>
<td></td>
</tr>
</tbody>
</table>

* IES, intracranial epilepsy surgery; LGS, Lennox–Gastaut syndrome; Prosp Obs, prospective observational; RCT, randomized controlled trial.

b At 6-month follow-up.
A final potential confound is the effect of AED regimen changes on seizure frequency over time in the setting of VNS. Many office visits were accompanied by VNS setting changes and, much more frequently, by AED regimen adjustments (medication and/or dosage changes). The complexity and frequency of such changes (often multiple changes in a single visit) proved too difficult to incorporate into a meaningful analysis. We could not control for all of these changes but believe AED treatment plays a major role in the success of any treatment plan that includes long-term VNS therapy. In fact, the increase in VNS efficacy over time reported by numerous centers [11–13, 17, 19, 26, 30] may be due to alteration in device parameters, changes in AED regimen, or an undefined, synergistic effect of both.

Despite these limitations, the merits of this study include the large number of patients (>400) and the lengthy follow-up duration (mean follow-up of nearly 5 years). Nevertheless, the conclusions drawn in this report may not be generalizable to all practices and patients. We stress that our treatment protocol and outcomes arise in the setting of a high-volume epilepsy center using a multidisciplinary approach. We agree with other centers [30, 34, 37] and stress that VNS—despite its apparent simplicity and safety—should be considered as a palliative treatment option for patients with TRE but only after thorough evaluation to exclude those patients who may benefit from and are willing to undergo intracranial surgery. Further study is needed to determine the overall benefit VNS provides in terms of quality of life for patients with TRE and whether a 50% reduction in seizure burden constitutes a meaningful improvement to most patients and caretakers.

5. Conclusions

Vagus nerve stimulation is a safe and effective palliative treatment option for focal and generalized TRE in adults and children. When used as part of a multimodality treatment plan including aggressive AED regimens and epilepsy surgery, more than 60% of patients with TRE experienced at least a 50% reduction in seizure burden. Good results were noted in patients with non-US FDA-approved indications; prospective, randomized trials are needed for patients with generalized epilepsies and for younger children to potentially expand the number of patients who may benefit from this palliative treatment.

Supplementary materials related to this article can be found online at doi:10.1016/j.yebeh.2010.10.017.

Ethical approval

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest statement

None of the authors has any conflicts of interest to report.

References

None of the authors has any conflicts of interest to report.

References