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Efficacy of vagus nerve stimulation over time: Review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS >10 years

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ABSTRACT

Objective: Studies have reported improved seizure control with increased duration of vagus nerve stimulation (VNS) but are prone to methodological biases. We analyzed the efficacy of VNS over time in patients with treatment-resistant epilepsy (TRE) who underwent VNS therapy 10 or more years.

Methods: We retrospectively reviewed 65 consecutive patients (29 females) who underwent VNS therapy ≥10 years. The mean age at VNS insertion was 30.0 years. Forty-four adults (≥18 years; 67.7%) and 21 children (32.3%) were included. Seizure frequency and antiepileptic drug (AED) regimens were recorded prior to VNS and, following VNS insertion, at 6 months, 1 year, 2 years, and every 2 years thereafter.

Results: The mean duration of VNS therapy for this group was 10.4 years, and the mean decrease in seizure frequency at last follow-up was 76.3%. The mean reduction in seizures at 6 months and years 1, 2, 4, 6, 8, and 10 years was 35.7, 52.1, 58.3, 60.4, 65.7, 75.5, and 75.5%, respectively. Seizure frequency was significantly reduced from baseline at each of the recorded intervals ($P<0.001$). There was a trend toward increased AED burden in the latter years of the follow-up period.

Conclusion: Following a "ramp-up" and accommodation period throughout the initial 24 months after VNS implantation, seizure control improved slightly over the subsequent years of therapy and eventually stabilized. Variation in seizure frequency, however, was common, and frequent changes in AED regimens or stimulation parameters were likely an important and possibly synergistic component of seizure control.

The most widely used neurostimulation for treatment-resistant epilepsy (TRE) is vagus nerve stimulation (VNS, VNS Therapy System, Cyberonics, Inc., Houston, TX, USA), which is approved by the U.S. Food and Drug Administration (USFDA) to treat patients with intractable partial epilepsy over the age of 12.

Randomized trials have demonstrated 25 to 30% reductions in seizure burden after 3 months of VNS therapy [1–3]. Nonblinded, nonrandomized studies have corroborated these findings and support the efficacy and safety of VNS in adults and children with generalized epilepsy [4–9]. Although some centers reported increased seizure control with increasing duration of VNS therapy [6,7,9–13], the methodologies do not establish this relationship.

We reviewed 65 consecutive patients who received VNS therapy for more than 10 years and analyzed the change in seizure control over time.

1. Methods

1.1. Subjects

Between November 1997 and April 2008, 507 patients underwent VNS operations at the New York University and Saint Barnabas Medical Center Comprehensive Epilepsy Centers by a single surgeon (W.K.D.). Seventy-one patients were referred for removal or revision of the VNS device originally implanted elsewhere by others; 436 consecutive patients with TRE underwent primary insertion of a VNS device. Eighty patients had their VNS devices implanted by the senior author more than 10 years prior to the termination of the collection of follow-up data. Fifteen patients did not receive VNS therapy for at least 10 years. Three patients had no follow-up data available; 6 patients died, and 6 patients had their devices removed before 10-year follow-up. The remaining 65 patients underwent VNS therapy for more than 10 years and are reported here.

At the initial office visit, all patients were prospectively entered into a clinical database. Data included demographic information, surgical history, physical and neurological examinations, epilepsy characteristics,

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Table 1
Demographic and clinical data for 65 patients who underwent VNS therapy >10 years for treatment-resistant epilepsy.

Variable	Number (%) or mean ± SD (range) [median]
Sex	
Female	29 (55.4%)
Male	36 (44.6%)
Age at seizure onset (years)	10.2 ± 11.3 (birth–55)
Duration of epilepsy prior to VNS	19.7 ± 11.0 (5 months to 47.1 years)
Age at VNS insertion (years)	30.0 ± 16.6 (6.7–73)
Children (≤18 years of age)	21 (32.3%)
Adults >18 years of age	44 (67.7%)
Median seizure frequency (per week)	4 (0.12–140)
Number of AEDs	2.8 ± 0.7 (0–4) [3]
AED burden (DDD-based)	2.7 ± 1.1 (0–5.7) [2.7]
Number of AEDs failed	6.0 ± 2.9 (1–13)
Prior failed intracranial epilepsy surgery	20 (30.8%)
Number of seizure types	2.0 ± 1.1 (1–5)
Developmental delay	33 (50.8%)

mean weekly seizure frequency (obtained from seizure logs), treatment history, and imaging findings. This report retrospectively analyzed this database.

Each patient underwent a presurgical evaluation that included history and physical, EEG, MRI, and, in most cases, video/EEG and functional imaging studies. Most patients were presented at a presurgical multidisciplinary conference and recommended for VNS insertion. Typical indications were multifocal or diffuse seizure onsets not amenable to surgical resection, persistent or recurrent seizures following intracranial epilepsy surgery, antiepileptic drug (AED) toxicity or intolerable side effects, medical unfitness for craniotomy, and patient or family preference for conservative measures prior to or in lieu of possible craniotomy.

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.

Table 2
Epilepsy classification, EEG findings, and etiology for 65 patients who underwent VNS therapy >10 years for treatment-resistant epilepsy.

Variable	Number (%)
Epilepsy classification	
Multifocal partial epilepsy (MFPE)	29 (44.6%)
Symptomatic generalized epilepsy (SGE)	13 (20.0%)
Idiopathic generalized epilepsy (IGE)	19 (13.5%)
MFPE/SGE	8 (12.3%)
Focal (frontal or temporal)	8 (12.3%)
EEG findings	
Multifocal	29 (44.6%)
Diffuse/generalized	32 (33.5%)
Diffuse/multifocal	8 (12.3%)
Focal	8 (12.3%)
Epilepsy etiology	
Idiopathic	30 (46.2%)
Cerebral palsy/static encephalopathy	5 (7.7%)
Neuronal migration disorders	2 (3.1%)
Infection	6 (9.2%)
Lennox–Gastaut syndrome	6 (9.2%)
Tuberous sclerosis complex	3 (4.6%)
Genetic/metabolic disorders	2 (3.1%)
Vascular lesion/tumor	4 (6.2%)
Traumatic brain injury	3 (4.6%)
Landau–Kleffner syndrome	2 (3.1%)
Hypothalamic hamartoma	2 (3.1%)

Table 3
Seizure control outcomes by modified Engel and McHugh outcome classifications for 65 patients who underwent VNS therapy >10 years for treatment-resistant epilepsy.

Class	Modified Engel description	Number (%)	McHugh description	Number (%)
I	Seizure free Rare, nondisabling simple partial seizures	16 (24.6%)	80–100% reduction in seizure frequency	36 (55.4%)
II	>90% reduction in seizure frequency Rare complex partial seizures	10 (15.4%)	50–79% reduction in seizure frequency	20 (30.8%)
III	50–90% reduction in seizure frequency	30 (46.2%)	<50% reduction in seizure frequency	6 (9.2%)
IV	<50% reduction in seizure frequency	9 (35.1%)	Magnet benefit only	0 (0%)
V	–	–	No improvement	3 (4.6%)

1.2. Surgical procedure and outcome assessment

The surgical techniques for subcutaneous and subpectoral implantation of the VNS device are described elsewhere [14]. Surgical follow-up typically occurred 2 weeks postoperatively and, subsequently, on a variable schedule as clinically indicated. Long-term follow-up and adjustments of VNS parameters were conducted by the epileptologist.

Retrospective chart review was performed to collect follow-up and outcome data. We recorded seizure frequency per week and AED regimen at presurgical baseline and following VNS implantation at 6 and 12 months, at 2-year intervals between years 2 and 10, and at the last follow-up visit. 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, the last office visit or inpatient admission was used as time of last follow-up. A standardized questionnaire addressing complications and side effects was completed at each follow-up visit at our centers.

Postoperative seizure outcomes assessed at the time of the last follow-up are expressed with a modified Engel scale [15] and with a VNS-specific outcome scale proposed by McHugh et al. [16].

Antiepileptic drug burden was assessed via two methods. In one method, the raw number of the drugs taken at each visit was tabulated, and in the second method, the dosage of each AED was taken into consideration. The World Health Organization (WHO) has established the "defined daily dosage" (DDD) for medications including AEDs as the

Table 4
Seizure control outcomes and AED use over time for 65 patients who underwent VNS therapy >10 years for treatment-resistant epilepsy.

Duration of VNS therapy	Number (%) with complete follow-up[a]	Seizure reduction			AED usage	
		Mean	95% CI	Median	Number (median)	Burden[b] (median)
6 months	55 (84.6%)	35.7%	26.2–45.2%	25%	3	2.7
1 year	51 (78.5%)	52.1%	44.1–60.1%	50%	3	2.7
2 years	53 (81.5%)	58.3%	48.7–67.9%	60%	3	2.8
4 years	59 (90.8%)	60.5%	51.1–70.0%	64%	3	3.2
6 years	57 (87.7%)	65.7%	56.3–75.1%	73%	3	3.2
8 years	58 (89.2%)	75.5%	68.6–82.5%	88%	3	3.1
10 years	65 (100%)	75.5%	69.5–81.4%	80%	3	3.0
Last follow-up	65 (100%)	76.3%	71.1–81.5%	80%	3	3.2

[a] Follow-up data concerning seizure frequency and AED usage were not available for every patient at every interval. We found no significant difference in terms of baseline characteristics, AED usage, or seizure reduction outcomes between patients with and without complete follow-up data at any period in this study.

[b] Composite value based on weighted averages of the "defined daily dosage" of each AED taken.

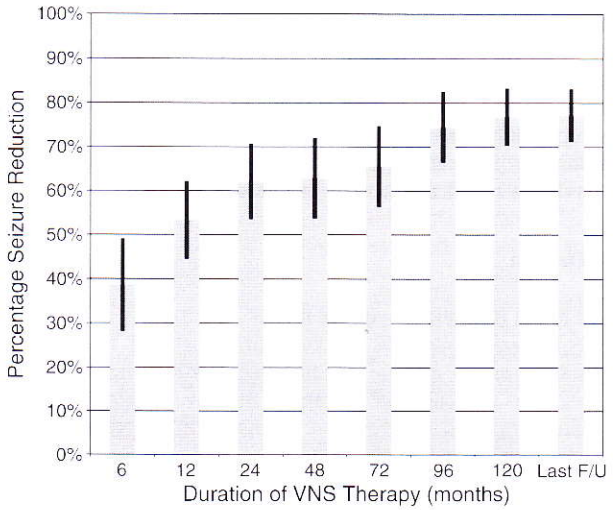

Fig. 1. Histogram illustrating mean percentage seizure reduction (gray bars), with 95% confidence intervals of the mean (vertical black lines), at serial follow-up visits after initiation of VNS therapy.

"assumed average maintenance dose per day for a drug used for its main indication in adults" [17]. Daily AED dosages were divided by the DDD for a given AED and used to calculate a weighted average that estimates total AED burden. For example, for a patient taking three AEDs,

$$\text{overall AED burden} = \text{dosage AED}_a / \text{DDD}_a + \text{AED}_b / \text{DDD}_b + \text{AED}_c / \text{DDD}_c.$$

We previously reported on our experience with subpectoral and subcutaneous VNS generator placement in 245 patients [14] and with VNS in 17 patients with tuberous sclerosis complex [18].

Vagus nerve stimulation therapy in patients with generalized epilepsies and children <12 years of age is an off-label usage not approved by the USFDA.

1.3. Statistical analyses

Measures of central tendency are expressed as means ± SD for parametric data and median values for nonparametric data. The crude number of pre- and post-VNS AEDs taken, the DDD-based AED burden, and seizure frequency were not normally distributed (nonparametric), and pre- and postoperative values were compared via paired-sample Wilcoxon signed ranks testing. Percentage seizure reduction was normally distributed, and Student's *t* test and ANOVA were used to compare differences in seizure reduction at different follow-up times.

Follow-up data were not complete for all patients at every follow-up point. For each period studied, we compared the baseline demographic, epilepsy, and AED data for patients with complete data with those for patients with incomplete data. We also compared percentage seizure reduction using the last follow-up data (complete for 100% of patients) between patients with and those without complete follow-up data at each period. Proportions were compared using Fisher's exact test; Mann–Whitney *U* testing was used to compare nonparametric data.

The raw data from the clinical database were entered into Microsoft Excel (Office 2008 for Mac). All statistics were calculated using SPSS 17.0 for Mac (SPSS Inc., Chicago, IL, USA). A two-tailed *P* value less than 0.05 was considered statistically significant.

2. Results

2.1. Patient demographics and seizure characteristics

Table 1 summarizes the baseline demographic and clinical data of all 65 patients. There were 29 females (55.4%) and 44 adults (67.7%). The mean age of patients at insertion was 30 years, and the mean duration of epilepsy before VNS therapy was 19.7 years. Patients were taking a median of 3 AEDs and had a DDD-based AED burden of 2.7 preoperatively. Thirty-three patients (50.8%) had developmental delay or significant cognitive deficits.

Table 2 summarizes the epilepsy classification, EEG findings, and etiology of seizures for all patients. The most common type of epilepsy was multifocal partial epilepsy (44.6%), and there was no identifiable etiology in 30 patients (46.2%).

2.2. Seizure control outcomes at last follow-up

The mean duration of VNS therapy was 10.4 ± 0.39 years (range: 10 years to 11.6 years). One patient died from status epilepticus; the remaining 64 patients are alive. The mean seizure reduction was 76.3% at the time of last follow-up. There was a significant decrease in median weekly seizure frequency from 4 prior to VNS to 0.5 at last follow-up ($P<0.001$).

There was no significant difference in the crude number of AEDs taken at time of last follow-up or any recorded interval (median number of AEDs: 3 at all times) when compared with preoperative baseline

Table 5
Seizure control outcomes as a function of duration of VNS therapy for treatment-resistant epilepsy.

Study	Number of patients	Design	3 months		6 months	
			Number (%) of patients	Median seizure reduction	Number (%) of patients	Median seizure reduction
George et al., 1994 [12]	31[a]	PO[b]	31 (100%)	39.5%	31 (100%)	40.8%
Murphy et al., 1999 [7]	60	R	60 (100%)	22.5%	–	32%
DeGiorgio et al., 2000 [11]	195	PO	–	37%	–	–
Helmers, et al., 2001 [6]	125	R	95 (76%)	51.5%	56 (44.8%)	51%
Amar et al., 2004 (A) [10]	921[c]	Registry	591 (64.2%)	42.5%	373 (40.5%)	42.9%
Amar et al., 2004 (B) [10]	3822[c]	Registry	2382 (62.3%)	47%	1547 (40.5%)	52.9%
Labar et al., 2004 [13]	269	Registry	269 (100%)	45%	–	–
Uthman et al., 2004[d] [19]	48	R	–	–	–	–
Current study[e]	65	R	–	–	55 (84.6%)	25%

[a] Original study group consisted of 31 patients who received high-stimulation and 38 patients who were randomized for low-stimulation. These patients were then followed prospectively and the results reported here are for the high-stimulation group.
[b] PO, prospective observational; R, retrospective.
[c] Group A failed prior intracranial epilepsy surgery; Group B had no history of epilepsy surgery.
[d] Mean, not median, percentage seizure reduction was reported. At 2-year follow-up, 38 patients were available for last visit carried forward analysis and had a mean reduction of 28%. Using declining-*n* analysis, 32 patients were considered to have a 42% decrease in seizure frequency.
[e] All patients had their devices turned on during the study period, but interim follow-up data concerning seizure frequency were not available at each time interval.

(median number of AEDs: 2.8). There was a greater AED burden (DDD-based) at last follow-up compared with baseline ($P<0.01$).

Table 3 summarizes the modified Engel and McHugh outcomes at last follow-up visit. At last follow-up, ≥90% seizure control was achieved by 24 patients (36.9%), ≥75% seizure control by 38 patients (58.5%), ≥50% improvement by 59 patients (90.8%), and <50% improvement by 6 patients (9.2%). Ten patients (15.4%) had been seizure free for at least 2 years prior to the last follow-up visit.

Six patients had intracranial epilepsy procedures following initiation of VNS therapy. Two patients had resections of seizure foci and subsequent reimplantation of VNS devices, two had complete callosotomies, and two had anterior thalamotomies. The latter four patients maintained their VNS devices during the cranial procedures.

2.3. Change in seizure frequency and antiepileptic drug usage over time

Table 4 summarizes percentage seizure reduction and number of patients with complete follow-up data at each time interval. Median weekly seizure frequency was reduced with VNS therapy at all recorded intervals (from 6 months to >10 years, $P<0.01$ in all comparisons). The mean seizure reduction at 6 months and years 1, 2, 4, 6, 8, and 10 was 35.7, 52.1, 58.3, 60.4, 65.7, 75.5, and 75.5%, respectively. Fig. 1 illustrates improved seizure control over time; note the plateau after 24 months of therapy with smaller gains after that period.

Table 4 summarizes the crude median number of AEDs taken and the DDD-based AED burden at each time interval. There was no difference in the crude number of AEDs taken preoperatively and at any later follow-up periods. Increased AED burden was noted beyond 8 years of VNS therapy ($P<0.03$ for all comparisons), and a marginally significant trend was noted between years 4 and 8 ($P=0.06$ for years 4 and 6).

We found no significant differences between the patients with and those without complete follow-up data at any time period in terms of baseline characteristics, AED usage or seizure reduction outcomes ($p>0.05$ for all comparisons).

2.4. Device revisions and removals

Sixty patients (92.3%) underwent a total of 75 VNS revisions after primary implantation at our center. Generator changes alone were performed in 70 cases, and complete VNS revision (generator and lead) in 5 cases. The most common indication for revision was generator power depletion and occurred at a mean of 52.2 ± 20.7 months following implantation or last generator change (range: 25–106 months). Lead fracture occurred in 5 devices and presented with delayed neck pain in synchrony with the stimulation duty cycle (4) or by loss of device efficacy (1).

Three patients (4.6%) underwent device removal following primary insertion at our center. Two patients had reinsertion after seizure focus resection. The last patient desired device removal for limited efficacy and has had a significant increase in seizure severity since removal.

3. Discussion

We found that seizure control improved with increasing duration of VNS therapy. Following 65 consecutive patients for more than 10 years, we noted a trend of improved seizure control over time that began to plateau after 2 years of therapy, with marginal gains between years 4 and 10. We found no change in the crude number of AEDs over this period. In the latter years of the follow-up period, an increase in the DDD-based calculation of AED burden, which takes the dosage of each medication into account, was noted.

3.1. Efficacy of vagus nerve stimulation over time

Preoperative predictors of long-term therapeutic response to VNS remain elusive. A common finding is that seizure control improves with increasing duration of VNS therapy [6,7,9–13]. Longer follow-up duration allows for titration of stimulation parameters beyond the narrow settings used in the initial randomized studies that were limited to only 3 months. In addition, most studies reporting increased VNS efficacy over time are plagued by methodological biases associated with retrospective data collection, nonresponder attrition (declining-*n* analyses), imprecision of last visit carried forward analyses, and relatively short follow-up durations [19]. Table 5 summarizes the major studies on VNS for TRE that report change in efficacy over time and the number of patients at each period.

George at al. [12] switched patients who were originally randomized to receive low stimulation to high stimulation after the original 3-month trial phase ended. They noted poorer response of the low-stimulation group, but these patients then experienced increased efficacy over time once they crossed over to high stimulation, paralleling the group who received high stimulation from the trial onset. Labar [13] compared seizure reduction at 3 and 12 months following initiation of VNS therapy in 269 patients identified from the Cyberonics, Inc. registry who remained on stable AED regimens. He reported improved median reduction of seizure frequency at 12 months (58%) compared

12 month		18 month		24 months	
Number (%) of patients	Median seizure reduction	Number (%) of patients	Median seizure reduction	Number (%) of patients	Median seizure reduction
30 (96.8%)	45.7%	26 (83.9%)	58.5%	–	–
–	–	46 (76.7%)	42%	–	–
–	46%	–	–	–	–
12 (9.6%)	51%	–	–	–	–
368 (40.0%)	45.7%	224 (24.3%	52.0%	156 (16.9%)	50.5%
1374 (35.9%)	60%	826 (21.6%)	62.7%	481 (12.6%)	66.7%
269 (100%)	58%	–	–	–	–
47 (97.9%)	26%	–	–	38 (79.2%)	28 vs 42%
51 (78.5%)	50%	–	–	53 (81.5%)	60%

with 3 months (45%). Patwardhan and colleagues [9] retrospectively analyzed reduction in seizure burden in 38 children treated with VNS therapy for a median of 1 year. They reported improved seizure control over time and a concomitant improvement in quality-of-life parameters as judged by caretakers using a simple visual analog scale.

Methodological biases aside, this phenomenon of improved seizure control with increasing duration of treatment for TRE has been reported with anterior thalamic stimulation [20] and levetiracetam [21]. There may be an ongoing effect of neural stimulation or certain medical treatments or, perhaps, regression to the mean.

The phenomenon of regression to the mean must always be considered when analyzing therapeutic impact. The frequency of an individual patient's seizures can naturally fluctuate. Many patients resort to treatment when disease severity is at or near its peak. Some component of seizure reduction may be a return to their baseline disease status or natural fluctuation, rather than a consequence of VNS treatment. Patients in this cohort had TRE for nearly 19 years prior to VNS and their seizures had failed to respond to an average of six AEDs alone or in combination, and seizures in almost one-third of patients failed to significantly improve from prior intracranial epilepsy surgery. Given such chronic and severe epilepsy, regression to the mean is an unlikely explanation for the majority of the treatment effect (mean reduction in seizure burden of 75%) as observed here over the course of 10 years of VNS therapy.

Another confounding concern is the unknown impact that changes in AED regimens have on seizure frequency over time in the setting of VNS. In our cohort, many office visits were accompanied by VNS setting changes and, more frequently, by AED regimen adjustments. Most VNS studies that address AED burden use the absolute number of AEDs taken at baseline and at follow-up visits. To our knowledge, a change in average AED intake with the addition of VNS therapy has been reported only in small series ($\leq$30 patients) [22–24]. Similar to other large series ($\geq$100 patients) [2,6,8,11,25,26], we found no difference in the crude number of AEDs taken before and after surgery.

We did note an increase in AED burden over time with analysis using the "daily defined dosages" index defined by WHO. This may contribute to the gradual reduction in seizure frequency over time seen in our VNS treatment cohort. Although this method yields a more precise measure of AED burden, there are still important limitations. The validity of the DDD and its clinical significance have not been established and it still fails to consider the side effect profile of each AED, a major factor in the decision to use a given medication and in the associated morbidity experienced by patients. The DDD system is also based on standard adult dosages and, therefore, may not be appropriate for calculating the AED burden for the 21 children (32.3%) in our cohort.

3.2. Comments on this study

The major limitation of this study is the retrospective nature of the data collection. Follow-up data concerning seizure frequency and AED use were not available for every patient at every time point. We attempted to account for the lack of complete follow-up data by showing there are no significant differences at any time point between patients with and without complete data in terms of baseline characteristics, AED usage, or percentage seizure reduction. This suggests that there was no systemic bias that explained the difference in seizure control outcomes at each period.

Determination of seizure frequency relied on reports from patients or caretakers and is inherently subject to error, a limitation with the majority of studies measuring seizure frequency and treatment outcomes. Seizure frequency was recorded as a composite value, which included different types of seizures (partial, generalized, drop attacks), prohibiting subgroup analysis of response by seizure type. Changes in device parameters over time were not consistently recorded, preventing assessment of the impact of stimulation changes on seizure frequency.

A design limitation inherent to all nonrandomized studies of VNS is the absence of a control group. Sparse data exist concerning the natural history of seizure severity and frequency in patients with TRE. Direct comparison of baseline and follow-up seizure frequency assumes that seizure frequency remains constant over time. This will misattribute reduced seizure burden as a consequence of VNS therapy, if there is regression to the mean associated with the natural history of a patient's epilepsy.

Although most studies discussed above are subject to responder attrition, ours is prone to responder retention; both can falsely elevate the perceived efficacy of VNS. The absolute value of percentage seizure reduction, however, was not the primary focus of this analysis. Rather we analyzed the trend in seizure control as a function of time in a group of consecutive patients. We could not control for all of the changes in AED regimens. Because our patients tended to have a greater AED burden in the latter years of the study, when seizure control was most pronounced, a firm conclusion related to long-term VNS efficacy is limited. However, longer-term titration of stimulation parameters and adjustments to the AED regimen may help maximize the effectiveness of VNS therapy over time [10], supporting the notion that VNS therapy has important long-term efficacy. Further study is needed to separate the roles of effective VNS titration, changes in AED regimen, potential synergy with AED regimens, and regression to the mean. Another important question that remains unanswered is whether the improved seizure control seen with VNS over time correlates with quality-of-life benefits for patients and their caregivers.

4. Conclusions

Following an initial "ramp-up" period and accommodation throughout the first 24 months following VNS implantation, seizure control tended to improve slightly over the course of years of therapy and eventually stabilized. Variation in seizure frequency, however, was common in this population, and frequent changes in AED regimens or stimulation parameters were likely an important and possibly synergistic component of seizure control.

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 conflict of interest to disclose.

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