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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.