

Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy

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BACKGROUND: Neuromodulation-based treatments have become increasingly important in epilepsy treatment. Most patients with epilepsy treated with neuromodulation do not achieve complete seizure freedom, and, therefore, previous studies of vagus nerve stimulation (VNS) therapy have focused instead on reduction of seizure frequency as a measure of treatment response.

OBJECTIVE: To elucidate rates and predictors of seizure freedom with VNS.

METHODS: We examined 5554 patients from the VNS therapy Patient Outcome Registry, and also performed a systematic review of the literature including 2869 patients across 78 studies.

RESULTS: Registry data revealed a progressive increase over time in seizure freedom after VNS therapy. Overall, 49% of patients responded to VNS therapy 0 to 4 months after implantation ($\geq 50\%$ reduction seizure frequency), with 5.1% of patients becoming seizure-free, while 63% of patients were responders at 24 to 48 months, with 8.2% achieving seizure freedom. On multivariate analysis, seizure freedom was predicted by age of epilepsy onset > 12 years (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.38-2.58), and predominantly generalized seizure type (OR, 1.36; 95% CI, 1.01-1.82), while overall response to VNS was predicted by nonlesional epilepsy (OR, 1.38; 95% CI, 1.06-1.81). Systematic literature review results were consistent with the registry analysis: At 0 to 4 months, 40.0% of patients had responded to VNS, with 2.6% becoming seizure-free, while at last follow-up, 60.1% of individuals were responders, with 8.0% achieving seizure freedom.

CONCLUSION: Response and seizure freedom rates increase over time with VNS therapy, although complete seizure freedom is achieved in a small percentage of patients.

KEY WORDS: Epilepsy, Outcome, Seizure freedom, Surgery, Vagus nerve stimulation

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Approximately 1% of the population has epilepsy, and seizures are refractory to antiepileptic drugs (AEDs) in approximately 30% of these individuals.¹ Many patients with drug-resistant temporal or extratemporal lobe epilepsy can become seizure-free with surgical resection or ablation, but other patients with epilepsy are not candidates for resection

given the presence of primary generalized seizures, nonlocalizable or multifocal seizure onset, or seizure onset from an eloquent brain region.²⁻⁵ Treatments based on neuromodulation, such as vagus nerve stimulation (VNS), have, therefore, become an increasingly important part of multimodal epilepsy treatment. VNS therapy was approved by the US Food and Drug Administration in 1997 as an adjunctive therapy for reducing seizures in patients with medically refractory epilepsy, and more than 80 000 patients have received treatment with VNS.⁶⁻⁸ The efficacy of VNS therapy has been evaluated by randomized controlled trials,^{9,10} retrospective case series,^{11,12} meta-analysis,¹³ and registry-based studies.¹⁴ These studies show that about 50%

ABBREVIATIONS: AED, antiepileptic drug; VNS, vagus nerve stimulation

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to 60% of patients achieve $\geq 50\%$ reduction in seizure frequency after 2 years of treatment, and response rates increase over time, likely related to neuromodulatory effects with ongoing stimulation.¹³ Complete seizure freedom, however, is less common with VNS therapy and other neuromodulation treatment modalities.

Given that a minority of patients achieve seizure freedom with VNS, rates and predictors of seizure freedom have not been well studied and remain poorly understood. The vast majority of studies that evaluate VNS therapy focus on rate of response over time (defined as $\geq 50\%$ reduction in seizures) and predictors of response; there has never been a large-scale evaluation of seizure freedom as a primary end point in patients treated with VNS. However, seizure freedom is the single best predictor of quality of life in patients with epilepsy,^{15,16} and therefore a better understanding of seizure freedom rates and predictors in patients treated with VNS therapy is critically needed. Importantly, this information may lead to improved patient selection and counseling in the treatment of drug-resistant epilepsy.

Here, we provide the first large-scale study of VNS therapy with a primary goal of defining seizure freedom rates and predictors, and comparing predictors of seizure freedom with those of overall response to treatment. Our study includes univariate and multivariate analyses of registry data including 5554 patients treated with VNS, and also includes a systematic review of the literature including 2869 patients across 78 studies, to help confirm registry-based results.

METHODS

Patient Outcome Registry Data Collection

Data were obtained from the VNS therapy Patient Outcome Registry maintained by the manufacturer of the device, Cyberonics, Inc. (Houston, Texas). This database was established in 1999, after US Food and Drug Administration approval of VNS therapy for epilepsy in 1997, to systematically monitor patient outcomes. Data were prospectively collected by 1285 prescribing physicians from 978 centers (911 in the United States and Canada and 67 internationally) at patients' preoperative baselines and at various intervals during therapy. During active data collection, participation in the registry included approximately 18% of all VNS devices implanted. The registry was institutional review board approved and patients provided consent.

Neurologists or their designees completed standard case report forms based on the patient's medical history or current visit and voluntarily sent these forms to Cyberonics for data entry. At baseline, a patient history and implant form was submitted that collected information on patient demographics, epilepsy etiology and syndrome, historical seizure types and frequencies, quality of life, physician global assessment, and current AEDs. Medication changes, malfunctions, battery changes, and changes in therapy were also tracked where possible at each time point of data submission. In between points of data submission, constant therapy since the previous data submission was assumed. Overall, 52% of patients in the registry were male, and the average age at implant was 27.3 years (median 26, range 0-87 years), with age < 12 years in 20% of patients, 12 to 18 years in 34%, 18 to 50 years in 37%, and age > 50 years in 9% of patients. The mean age of epilepsy onset was 8 years (median 4, range 0-85 years), and the average number of current AEDs at implant was

2.5 (median 2, range 0-5), with 87% of patients on 2 or more AEDs. Patients had a localized epilepsy syndrome in 59%, generalized epilepsy in 27%, and had Lennox-Gastaut or a similar syndrome in 11%. Previous investigators have authenticated the integrity of the systems for collecting and processing registry data using an independent auditing agency.¹⁷

The database was queried in January 2015, and all seizure outcomes reported with the 0- to 4-, 4- to 12-, 12- to 24-, and 24- to 48-month time ranges after VNS device implantation were extracted and compared with patient preoperative baseline. Overall percent decrease in seizure frequency compared with baseline and response rates to VNS therapy were also calculated at each follow-up visit using the seizure rates reported by the treating neurologist at each visit. Patients with $\geq 50\%$ decrease in seizure frequency after VNS therapy compared with preoperative baseline were designated "responders," while those with $< 50\%$ reduction in seizure frequency were labeled "nonresponders." Seizure freedom in the present study was defined as complete freedom of all seizures (seizure frequency of 0) at a specified time point, corresponding to class Ia outcome using the Engel outcome classification scheme.¹⁸ Of note, unlike a randomized controlled trial or prospective study that would mandate follow-up for each patient at each time point, attrition in the registry leads to a significantly smaller sample size at later follow-up time points, which may lead to selection bias.

Other information collected in the registry at each follow-up visit included sex, race, age at diagnosis and implantation, preoperative duration of epilepsy, seizure types, seizure frequency (overall and by seizure type), current AEDs, and epilepsy etiology. Seizure types classified as "generalized" included primary and secondarily generalized tonic-clonic, atonic (drop attacks), and absence seizures, while those classified as "partial" (focal) seizures included complex partial (focal with impairment of consciousness) and simple partial (focal without impairment of consciousness), including auras. Epilepsy etiologies classified as "lesional" included tumor, cyst, vascular malformation, tuber, mesial temporal sclerosis, and malformation of cortical development, while those classified as "nonlesional" included postinfectious, postischemic, inflammatory, Lennox-Gastaut or similar infantile syndrome, posttraumatic, cerebral palsy/perinatal event, or unknown/idiopathic. Although complications were not examined as a primary end point in the present study, previous large prospective studies have reported transient hoarseness or change in voice as the most common side effect in one-third to one-half of patients, infection in 3% to 4% of cases, and other possible adverse events including cough, paresthesia, pain, dyspnea, or headache.^{7,10,19} Similarly, although the cost of VNS therapy was not a focus of this study, previous cost-utility analyses have been reported and have typically demonstrated cost savings with VNS compared with continued medical therapy for intractable epilepsy.^{20,21}

Systematic Literature Review

To help support registry-based results, a systematic review of the literature was performed, as summarized in the **Figure, Supplemental Digital Content** (<http://links.lww.com/NEU/A821>). The literature search was conducted in January 2015 using PubMed, and resulted in 639 citations. The search terms included (vagus[ti] OR vagal[ti] OR VNS[ti]) AND epilepsy, with filters for human and English. In addition, the references of several relevant review articles were examined, resulting in the identification of an additional 12 articles, leading to 651 total citations for preliminary review. An initial abstract review was then conducted, and 466 articles were eliminated for the following reasons: incomplete data to determine seizure freedom rate (no outcomes

reported; electroencephalography data only; inflammation data only; rating scale validation; vagus nerve modeling; surgical technique; adverse events only; magnetoencephalography compatibility); non-English; non-human; non-peer-reviewed (supplement, editorial, guidelines); review article; non-VNS; nonepilepsy; registry data; patient survey; and status epilepticus. The remaining 185 articles were included for review, and a second phase of elimination was conducted by examining the full article. An additional 107 articles were excluded for the following reasons: incomplete data to determine seizure freedom rate (no outcomes reported; data in text does not match data in table; reports by seizure type, not patient; seizure freedom not reported); duplicate patients; non-VNS therapy; status epilepticus; and registry/supplement/review. In total, 78 articles were included in the literature review of this article.^{11,22-31,32-51,52-71,12,72-97}

Of these studies, Cyberonics provided direct funding for pre- or postmarket trial activities in 14 (18%) studies, and 3 (4%) reports received editorial support by Cyberonics.

Articles were evaluated for seizure freedom rates. Five follow-up periods were used: 0 to 4 months, 4 to 12 months, 12 to 24 months, 24 to 48 months, and greater than 48 months. These time ranges resemble those most commonly used in the literature.^{98,99} If a study included data for the same patient during more than 1 follow-up period, multiple data points for the same patient were allowed. However, if a study included multiple data points for the same patient within the same follow-up period, only the last data point was used. For example, if data for a patient were reported at 1 month, 3 months, 6 months, 12 months, and 18 months, the 3-month data would be used for the first follow-up period, 6-month data for the second follow-up period, and the 18-month data would be used for the third follow-up period, with other data points being excluded.

Statistical Analysis of Registry Data

Univariate analysis was used to compare seizure freedom status (Pearson χ^2 test), responder status (χ^2), and median seizure frequency reduction (Wilcoxon sum rank test) between patients with primarily partial vs generalized seizure types, age <12 vs \geq 12 years old at implant, age <12 vs \geq 12 years old at epilepsy onset, male vs female sex, race category, and lesional vs nonlesional epilepsy. Multivariate analyses of these factors were performed using binary logistic regression with backward elimination of factors, with the primary end point being the presence or absence of seizure freedom, or the presence or absence of response to treatment at the 12- to 24-month follow-up period. The level of significance was set at 0.05 for all analyses. Statistical analysis was performed using JMP 10.0 and SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Query of the VNS Patient Outcome Registry resulted in data from 12 319 unique provider visits among 5554 patients. Of these, analysis included 4666 visits during the 0- to 4-month follow-up period after device implantation, 3277 visits at 4 to 12 months, 3182 visits at 12 to 24 months, and 1194 visits at 24 to 48 months. Duplicate visits for the same patient within the same follow-up period were excluded.

A progressive increase in the rate of seizure freedom, rate of response to treatment, and median decrease in seizure frequency were observed over time (Figure 1A). Specifically, 49% of patients responded to VNS at 0 to 4 months after implantation, with

5.1% of patients becoming seizure-free (median seizure reduction = 47%), while 63% of patients were responders at 24 to 48 months, with 8.2% of patients achieving seizure freedom (median seizure reduction = 63%). When comparing patients with predominantly partial seizures (Figure 1B) with those with predominantly generalized seizures (Figure 1C), seizure freedom was significantly more likely in those with generalized seizures at 0 to 4 months ($P < .01$, Pearson χ^2) and at 4 to 12 months ($P < .01$), although this difference was not significant at 12 to 24 months or 24 to 48 months ($P > .5$). Responder rate and median seizure reduction did not differ significantly between patients with predominantly partial vs generalized seizures.

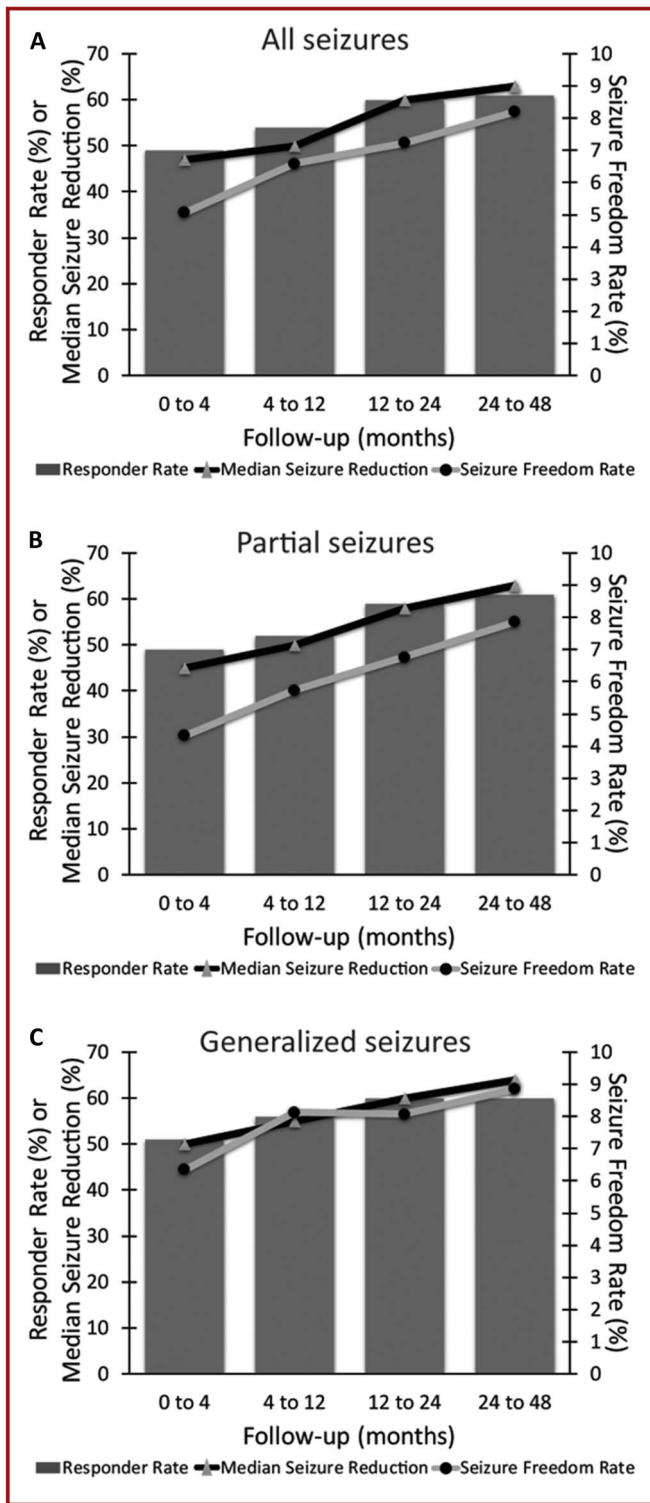
Patients who achieve seizure freedom after VNS therapy had significantly later onset of epilepsy than those with persistent seizures at all follow-up visits ($P < .05$ at each time point, Wilcoxon sum rank test), as summarized in Figure 2. At the last follow-up (24-48 months), 11.3% of patients \geq 12 years old at epilepsy onset were seizure-free, while only 7.3% of individuals <12 years old at epilepsy onset achieved this outcome (Figure 2A). However, no relationship was observed between age of implantation and seizure freedom rate (Figure 2B). This resulted in a trend in which patients receiving VNS <10 years after the onset of epilepsy had a higher rate of seizure freedom (10.4% at 24-48 months) than those implanted \geq 10 years after epilepsy onset (7.3% at 24-48 months), but this difference did not achieve statistical significance (Figure 2C).

Univariate analysis of other factors, including sex, race, and lesional vs nonlesional epilepsy, did not reveal significant differences in seizure freedom rates, with 1 exception: males were more likely than females to be seizure-free ($P < .01$, χ^2 test), but only at a single follow-up period (4-12 months). Multivariate analysis revealed that seizure freedom was significantly predicted by age of epilepsy onset >12 years, and predominantly generalized seizure type (Table), while overall response to VNS therapy was predicted by nonlesional epilepsy etiology (Table).

A systematic literature review of seizure freedom rates of patients treated with VNS therapy was also performed. A total of 2869 patients across 78 studies were included in the analysis.^{11,22-31,32-51,52-71,12,72-97} A progressive increase in both seizure freedom and overall response to treatment was observed over time in the literature (Figure 3), supporting results from the registry study (Figure 1A). Specifically, at the earliest (0-4 months) follow-up, 40.0% of patients had responded to VNS, with 2.6% becoming seizure-free, while at the latest time point (>48 months), 60.1% of patients were responders, with 8.0% achieving seizure freedom (Figure 3).

DISCUSSION

The present study represents the first large-scale evaluation of seizure freedom rates and predictors of response to VNS therapy for patients with drug-resistant epilepsy, including both registry-level analysis and systematic review. After device implantation, a progressive increase in seizure freedom was observed among 5554 patients in the VNS Patient Outcome Registry, consistent

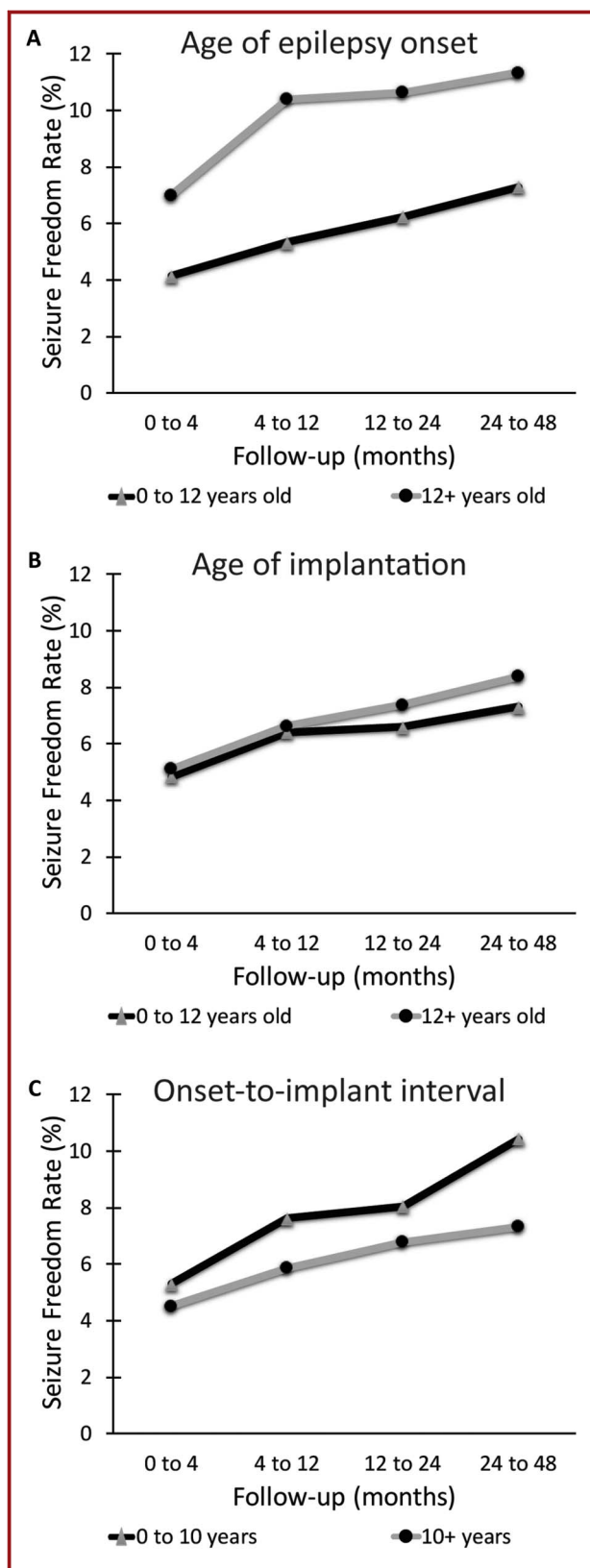


with the known increase in overall response to treatment over time that has been previously well described.^{9,10,13} Two to 4 years after implantation, approximately 8% of patients achieved complete seizure freedom, while approximately 60% of patients had responded to treatment, showing $\geq 50\%$ decrease in seizure frequency. Very similar rates of seizure freedom and overall response were observed in a systematic literature review of 2869 patients across 78 studies, supporting the registry-level data. Although data beyond 4 years of treatment were not available in the registry, the literature review results suggested additional increases in seizure freedom rates and response to treatment may be possible. These results suggest that both response rates and seizure freedom rates increase over time with VNS therapy, although complete seizure freedom is achieved in only a minority of patients. Interestingly, in multivariate analysis of registry data, while seizure freedom was predicted by age of epilepsy onset >12 years and predominantly generalized seizure type, overall response to treatment was predicted by nonlesional epilepsy etiology. This suggests that different factors may be associated with response to treatment compared with seizure freedom for patients treated with VNS therapy.

Our results confirm that complete seizure freedom is less common with VNS than resective epilepsy surgery. This is also the case with other neuromodulatory treatments for refractory epilepsy, as we have previously reviewed.¹⁰⁰ Therefore, current neuromodulation techniques are not replacements for resection for intractable focal epilepsy, and indeed, surgical resection for localizable epilepsy remains dramatically underutilized.¹⁰¹⁻¹⁰³ However, many patients with epilepsy are not candidates for resection or ablation, including those with a primary generalized epilepsy subtype, poorly localized seizures, multifocal seizure onset, or seizures originating in eloquent brain.⁵

Response to VNS therapy in the present study was found to be higher in patients with nonlesional epilepsy. Prior research has also suggested improved response to VNS with nonlesional epilepsy subtypes,^{13,14} and patients with nonlesional epilepsy are also less likely to be candidates for resection.^{3,104} It is not fully understood why patients with nonlesional epilepsy respond somewhat better to VNS, while in resective temporal or neocortical epilepsy

FIGURE 1. Seizure freedom, response to treatment, and median seizure reduction from the VNS therapy registry. Across all patients together (A), a progressive increase in seizure freedom was observed after device implantation, paralleling increases in the rate of response to therapy (defined as patients with $\geq 50\%$ seizure frequency reduction) and the median reduction of seizure frequency. When comparing patients with partial seizures (B) vs generalized seizures (C) as the predominant seizure type, seizure freedom was significantly more likely in patients with generalized seizures at 0 to 4 months ($P < .01$, Pearson χ^2) and at 4 to 12 months of follow-up, although this difference was not significant at 12 to 24 months or 24 to 48 months ($P > .5$). Responder rate and median seizure reduction did not differ significantly between patients with primarily partial vs generalized seizures. $N = 12319$ visits among 5554 patients, including 4666, 3277, and 3182, and 1194 patients at each follow-up period, respectively. VNS, vagus nerve stimulation.



surgery, patients with nonlesional epilepsy experience less favorable seizure outcomes.^{3,4,105,106} Our group and others have shown that, in resective surgery for many lesions, such as tumors or vascular malformations, gross-total resection is the single most important predictor of postoperative seizure freedom.^{104,107-111}

Therefore, perhaps the persistent presence of a defined, epileptogenic lesion irritates perilesional parenchyma and drives continued seizures when the lesion is only partially removed (as in subtotal resection) or is not removed at all (as in VNS). It is also likely that some of the more challenging lesional epilepsy cases go on to receive VNS, while the more favorable candidates undergo resection, which may skew seizure outcome data.

Seizure freedom in patients treated with VNS therapy was also noted to be more common in patients with primarily generalized seizures, as has been previously described.¹³ Importantly, patients with generalized epilepsy are also less likely to be candidates for resection. VNS, and other neuromodulation techniques, may therefore be considered in patients who are poor surgical candidates, in order to decrease seizure frequency. Finally, while it is possible that some patients who became seizure-free with VNS in the present study would have achieved this outcome with medication change or observation alone, prior studies suggest that only about 0% to 3% of patients in whom treatment with ≥ 2 AEDs has failed will achieve seizure freedom with further drug trials. In a pivotal study of patients newly diagnosed with epilepsy by Kwan and Brodie,¹¹² 47% of individuals became seizure-free after 1 drug, and an additional 14% stopped having seizures after a second drug, but only 3% of patients became seizure-free after a third or subsequent drug trial. In a recent randomized controlled trial of early resection in patients with < 2 years of refractory epilepsy, 0 of 23 patients assigned to continued medical optimization achieved seizure freedom with drug adjustments alone.¹¹³ Given that individuals who have continued seizures after treatment with ≥ 2 AEDs has failed are very unlikely to achieve seizure freedom with medical treatment alone, guidelines recommend that these patients be referred to a comprehensive epilepsy center for further evaluation and possible surgical intervention.¹¹⁴⁻¹¹⁶

Limitations

It is important to acknowledge several limitations of the present study. First, registry data were derived from a database sponsored

FIGURE 2. Seizure freedom rates by age of epilepsy onset and implantation. **A**, patients who achieve seizure freedom had significantly later onset of epilepsy than those with persistent seizures at 0 to 4 ($P < .001$, Wilcoxon sum rank test) 4 to 12 ($P < .001$), 12 to 24 ($P < .001$), and 24 to 48 ($P < .05$) months. **B**, no significant difference in age of implantation was observed between patients with or without seizure freedom ($P > .2$ at each time point, Wilcoxon sum rank test). **C**, patients who achieved seizure freedom showed shorter onset-to-implant intervals than those with persistent seizures, but this difference was not significant (P range 0.07-0.26 at each time point, Wilcoxon sum rank test). $N = 12319$ visits among 5554 patients, including 4666, 3277, and 3182, and 1194 patients at each follow-up period, respectively.

TABLE. Predictors of Seizure Freedom or Response to Treatment From Multivariate Analysis^{a,b}

	OR	95% CI
Seizure freedom		
Age of epilepsy onset >12 y	1.89	1.38-2.58
Predominantly generalized seizures	1.36	1.01-1.82
Response to treatment		
Nonlesional epilepsy	1.38	1.06-1.81

^aCI, confidence interval; OR, odds ratio.
^bResults of logistic regression analysis.

by Cyberonics, the manufacturer of VNS therapy. This conflict of interest may lead to data bias, and this must be carefully considered in the interpretation of these results. However, Amar and colleagues¹⁷ have previously authenticated the integrity of the systems for collecting and processing this registry data utilizing an independent auditing agency. Next, given the nature of patient registries, we are unable to independently confirm the validity of data submitted by individual physicians, and patient data in the registry represent only a minority of the total number of patients implanted with VNS. Furthermore, patient attrition in the registry leads to a significantly smaller sample size at later follow-up time points. For both of these reasons, possible selection bias and reporting inaccuracy must be carefully considered. However, the present study also includes a systematic literature review that excluded all registry-based studies, and those results closely

resemble findings from the registry analysis. Of note, predictors of seizure freedom were not examined in the literature review, because the nature of meta-analysis prevents multivariate analysis of variables that are not fully disaggregated. It should also be noted that of the 78 studies included in the literature review, Cyberonics contributed direct funding for pre- or postmarket trial activities in 14 (18%) studies, and another 3 (4%) reports received editorial support by Cyberonics. Finally, given that the present study provides level IV clinical data, our findings alone should not be used as practice guidelines. Further prospective study is warranted to confirm predictors of seizure freedom seen in our registry-based analysis. Notably, however, although both registry-based studies and systematic literature reviews provide data of lower quality than randomized controlled trials, the strength of the present evaluation lies in the ability to pool an extremely large number of patients that would be difficult to achieve even in a multi-institutional trial.

CONCLUSION

Patients with epilepsy in whom 2 or more AEDs have failed should be considered drug resistant and referred to a comprehensive epilepsy center for surgical evaluation. Although seizure freedom is more likely with resection than neuromodulation techniques, such as VNS therapy, certain patients are not candidates for resection, and neuromodulation should then be considered. After 2 to 4 years of VNS therapy, approximately 8% of patients achieve seizure freedom, and approximately 60% have responded to treatment. Although patients who have nonlesional epilepsy or generalized epilepsy are less likely to be candidates for surgical resection, these factors may actually portend improved outcomes with VNS.

Disclosures

Supported in part by the National Institutes of Health (F32-NS086353 to Dr Englot). Dr Wright and K. H. Hassnain are employees and Dr Wright is a shareholder of Cyberonics, the manufacturer of VNS therapy and sponsor of the VNS therapy Patient Outcome Registry. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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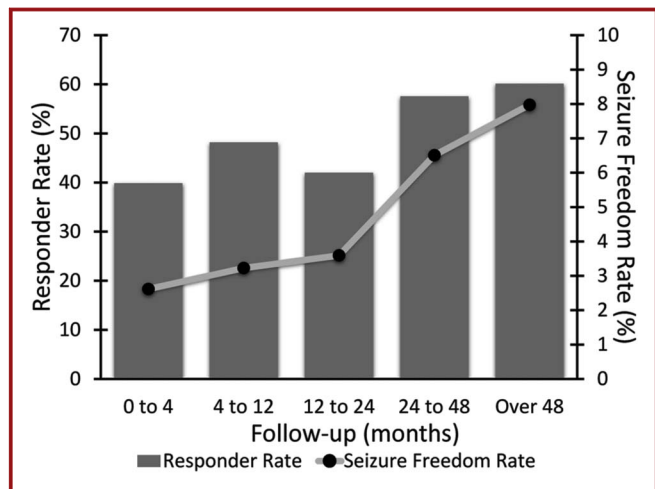


FIGURE 3. Seizure freedom and response rate with VNS from systematic literature review. Data compiled from 2869 patients across 78 studies in the systematic review show progressive increase in both seizure freedom and response rate over time, resembling findings from the registry (Figure 1). At latest follow-up, 60% of patients responded to VNS (≥50% reduction in seizures), and 8% were seizure free. N = 650, 405, 1503, 876, and 326 patients at each follow-up period, respectively. VNS, vagus nerve stimulation.

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COMMENT

The authors examined 5554 patients from the VNS therapy patient outcome registry, and also performed a systematic review of the literature including 2869 patients across 78 studies. The authors conclude that after 2 to 4 years of VNS therapy, approximately 8% of patients achieve seizure freedom, and about 60% have responded to treatment.

Congratulations to the authors for this interesting and well-written article. The mentioned registry has been very controversial over the years, in terms of its validation, enrollment, inclusion criteria, type of follow-up, and large number of drop-offs. In addition, conflict of interest has been a concern, since the registry is funded by the company. Consequently, a thoughtful and critical interpretation of the current results is fundamental to clarify the indications and expected results of vagal nerve stimulation therapy in patients with medically intractable epilepsy who are not candidates for resective surgery. The article reinforces the perception that some patients do gain benefit from this palliative method.

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