12-1-2015

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Recommended Citation

Wasade VS, Schultz L, Mohanarangan K, Gaddam A, Schwalb JM, and Spanaki-Varelas M. Long-term seizure and psychosocial outcomes of vagus nerve stimulation for intractable epilepsy. Epilepsy Behav 2015; 53:31-36.

Epilepsy & Behavior 53 (2015) 31–36

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Long-term seizure and psychosocial outcomes of vagus nerve stimulation for intractable epilepsy

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ARTICLE INFO

Article history:
Received 22 August 2015
Revised 19 September 2015
Accepted 21 September 2015
Available online 26 October 2015

Keywords:
Epilepsy
Vagus nerve stimulation or VNS
Long-term
Outcome
Seizure
Psychosocial

ABSTRACT

Vagus nerve stimulation (VNS) is a widely used adjunctive treatment option for intractable epilepsy. Most studies have demonstrated short-term seizure outcomes, usually for up to 5 years, and thus far, none have reported psychosocial outcomes in adults. We aimed to assess long-term seizure and psychosocial outcomes in patients with intractable epilepsy on VNS therapy for more than 15 years. We identified patients who had VNS implantation for treatment of intractable epilepsy from 1997 to 2013 at our Comprehensive Epilepsy Program and gathered demographics including age at epilepsy onset and VNS implantation, epilepsy type, number of antiepilepsy drugs (AEDs) and seizure frequency before VNS implantation and at the last clinic visit, and the most recent stimulation parameters from electronic medical records (EMR). Phone surveys were conducted by research assistants from May to November 2014 to determine patients' current seizure frequency and psychosocial metrics, including driving, employment status, and use of antidepressants. Seizure outcomes were based on modified Engel classification (I: seizure-free/rare simple partial seizures; II: >90% seizure reduction (SR), III: 50–90% SR, IV: <50% SR; classes I to III (>50% SR) = favorable outcome). A total of 207 patients underwent VNS implantation, 15 of whom were deceased at the time of the phone survey, and 40 had incomplete data for medical abstraction. Of the remaining 152, 90 (59%) were contacted and completed the survey. Of these, 51% were male, with the mean age at epilepsy onset of 9.4 years (range: birth to 60 years). There were 35 (39%) patients with extratemporal epilepsy, 19 (21%) with temporal, 18 (20%) with symptomatic generalized, 5 (6%) with idiopathic generalized, and 13 (14%) with multiple types. Final VNS settings showed 16 (18%) patients with an output current >2 mA and 14 (16%) with rapid cycling. Of the 80 patients with seizure frequency information, 16 (20%) had a modified Engel class I outcome, 14 (18%) had class II, 24 (30%) had class III, and 26 (33%) had class IV. Eighty percent said having VNS was worthwhile. Among the 90 patients, 43 patients were ≥18 years old without developmental delay in whom psychosocial outcomes were further analyzed. There was a decrease in the number of patients driving (31% vs 14%, $p = 0.052$) and working (44% vs 35%, $p = 0.285$) and an increase in the number of patients using antidepressant medication (14% vs 28%, $p = 0.057$) at the time of survey compared to before VNS. In this subset, patients with >50% SR (60%) were taking significantly fewer AEDs at the time of survey compared to patients with unfavorable outcomes (median: 3 vs 4, $p = 0.045$). The associations of >50% SR with the psychosocial outcomes of driving, employment, and antidepressant use were not significant, although 77% of this subset said VNS was worthwhile.

This is the first study that assesses both seizure and psychosocial outcomes, and demonstrates favorable seizure outcomes of >50% SR in 68% of patients and seizure freedom in 20% of patients. A large majority of patients (80%) considered VNS therapy worthwhile regardless of epilepsy type and psychosocial outcomes.

1. Introduction

Almost 30% of all epilepsies remain intractable to antiepilepsy drugs (AEDs) [1], and adjunct nonpharmacologic therapies that include surgical treatment options, stimulation therapies, and ketogenic or alternative medical therapies are often explored in those cases. Since 1997, VNS (by VNS Therapy Systems, Cyberonics, Inc., Houston, TX, USA) has been approved by the U.S. Food and Drug Administration (FDA) as an

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http://dx.doi.org/10.1016/j.yebeh.2015.09.031

adjunctive therapy for treatment of intractable epilepsy, and short-term efficacy has been established through a randomized controlled trial [2]. Subsequent studies have reported seizure outcomes for up to 5 years [3–7] and rarely to 10–11 years [8,9]. A few studies have assessed behavioral and cognitive outcomes after VNS therapy in children [10] and the effect on mood in adults [11]. However, thus far, no data assessing common psychosocial outcomes are available in adults. The aim of our study was to assess long-term seizure and psychosocial outcomes for more than 15 years in all patients with intractable epilepsy who had VNS implantation at our tertiary epilepsy center by conducting follow-up phone surveys. This study was, to some extent, a continuation of the assessment of long-term outcomes of surgical therapies for intractable epilepsy at our center [12].

2. Materials and methods

2.1. Study description, approvals and consents

This was a retrospective study on patients with intractable epilepsy to gather pre-VNS implantation information and a cross-sectional study to assess postimplantation seizure and psychosocial outcomes. Patients who had VNS implantation for intractable epilepsy from 1997 to 2013 were retrospectively identified. Data were collected using medical record chart reviews and phone surveys. Low-risk, retrospective methodologies of the chart review led to waiving of written consents. Prior to starting every phone survey, verbal consents were obtained. This study was approved by the Henry Ford Health System Institutional Review Board (IRB # 8835).

2.2. Data collection

Demographic information consisting of gender, age and race, age at epilepsy onset and VNS implantation, epilepsy type, number of AEDs used, and seizure frequency before VNS implantation were collected by retrospective chart reviews using the EMR. Clinical notes from the last visit in EMR were reviewed to obtain information on the most recent seizure frequency and stimulation parameters. The Department of Public Health Sciences obtained patient contact information from EMR or through a public search database. The research assistants (KM, AG) attempted follow-up phone surveys for all the patients from May to November 2014. A script that included confidentiality statements along with questions about the patients' current seizure frequency, the current number of AEDs being taken, and queries on psychosocial metrics was followed by the research assistants during the phone survey. In our experience, phone surveys had a potential for a better response rate, especially given that a number of the patients may have moved out of the area and/or were not receiving their care at our institution, and hence were chosen over mailed or in-person surveys. The selection of the psychosocial metrics of driving, employment, and antidepressant use were chosen as by Dupont et al. [13] and was also based on our experience with patients with epilepsy demonstrated in postsurgical outcomes [12]. Patients who were deceased at the time of survey and those who refused to participate or could not be contacted despite at least three phone attempts were not included in the final outcome assessment.

We aimed to assess the effect of some VNS stimulation parameters on the therapeutic response [14] by assessing seizure outcomes. We considered current stimulation of more than 2 mA as a cutoff for higher intensities as a lower current was safer and better tolerated [15], as in our clinical experience. Duty cycle was calculated (ON time + 4/ON time + OFF time) for each of the VNS settings and the ratio of more than 25% was considered as rapid cycling in our study, as duty cycles of 50% or less are typically known to be safe and effective [14].

2.3. Outcome assessment

Seizure outcomes after VNS implantation were based on modified Engel classification [16], and classes I to III were considered as favorable outcomes with SR of >50% (Table 1). This classification was based on the patients' responses to questioning about seizure frequency at the time of survey compared to before VNS implantation. Psychosocial metrics assessed on the phone survey included driving status, employment status (full-time, part-time, or unemployed) and the use of antidepressant medications before VNS and at the time of survey. Patients' satisfaction was assessed by asking them if it was worthwhile having VNS as an adjunctive treatment for intractable epilepsy.

2.4. Statistical analysis

To assess the associations of survey response, epilepsy type, and favorable outcomes with demographics, VNS stimulation parameters, and psychosocial measures, chi-square tests were used for the binary or categorical variables, two-sample t-tests were used for the continuous measures of age at onset and age at VNS implantation, and Wilcoxon two-sample tests were used for number of years between epilepsy onset and VNS implantation, number of seizures per month before VNS, number of AEDs before VNS, and duration of VNS therapy. McNemar's tests were done to compare preoperative to postoperative responses for driving, employment, and use of antidepressants. Statistical significance was set at the 0.05 level. Statistical analyses were performed using SAS version 9.2.

3. Results

3.1. Description of identified patients

A total of 207 patients with epilepsy were identified as having VNS implantation between 1997 and 2013. Fifteen patients were confirmed to be deceased, and 40 had incomplete data for medical abstraction. Of the remaining 152 patients, 90 (59%) were contacted and agreed to complete the phone survey, 14 (9%) refused to participate, and 48 (32%) of the patients could not be contacted (21 with wrong or no phone numbers, 22 with no answer, and 5 repeatedly postponed answering the survey) after at least three attempts on different days and different times. Ten patients could not have modified Engel classifications because of missing information for frequency of seizures prior to VNS or at the time of the survey. Of the 152 eligible patients, 53% (n = 80) were male, 100 (66%) were Caucasian, and 15 (10%) were African American. The mean age at epilepsy onset was 9.7 years (range: birth to 60 years). The mean duration of epilepsy before VNS was 20.5 years (range: 3 to 54 years).

3.2. Medical record and survey

Comparisons of demographic, medical, and surgical variables between patients with and without completed surveys were performed in order to assess any potential responder bias (Table 2). No differences were detected for gender, race, age at epilepsy onset, age at VNS implantation, duration between epilepsy onset and VNS implantation, presence

Table 1
Seizure outcomes by modified Engel classification for 80 patients with intractable epilepsy on VNS therapy.

Class	Modified Engel description	Number (%)
I	Seizure-free Rare, nondisabling simple partial seizures	16 (20%)
II	>90% reduction in seizure frequency Rare complex partial seizures	14 (18%)
III	50–90% reduction in seizure frequency	24 (30%)
IV	<50% reduction in seizure frequency	26 (33%)

Table 2
Comparison of patients who did and did not complete the survey.

Variable	Response	Survey completed (N = 90)	No survey (N = 62)	p-Value
Gender	F	44 (49%)	28 (45%)	0.651
	M	46 (51%)	34 (55%)	
Race	African American	6 (7%)	9 (15%)	0.448
	Caucasian	62 (69%)	38 (61%)	
	Other	5 (6%)	3 (5%)	
	Unknown	17 (19%)	12 (19%)	
Age at epilepsy onset	Mean ± S.D.	9.4 ± 11.9	10.3 ± 12.1	0.669
	Median (range)	5 (0 to 60)	4.5 (0 to 41)	
Age at VNS	Mean ± S.D.	31.1 ± 14.1	31.2 ± 15.0	0.964
	Median (range)	30.5 (5 to 65)	33 (4 to 67)	
Years between epilepsy onset and VNS implantation	Mean ± S.D.	20.7 ± 12.7	20.2 ± 10.4	0.938
	Median (range)	18 (3 to 54)	17.5 (4 to 41.33)	
Developmental delay	Yes	44 (49%)	31 (51%)	0.816
	No	46 (51%)	30 (49%)	
Presence of status epilepticus before VNS	Yes	13 (15%)	7 (12%)	0.587
	No	75 (85%)	53 (88%)	
Resective epilepsy surgery performed	Yes	28 (31%)	10 (17%)	0.052
	No	62 (69%)	49 (83%)	
Number of seizures per month before VNS	Mean ± S.D.	50.9 ± 108.2	166.7 ± 514.9	0.129
	Median (range)	12.75 (0.33 to 600)	17.5 (1 to 3600)	
Number of AEDs before VNS	Mean ± S.D.	3.0 ± 1.0	2.8 ± 1.1	0.207
	Median (range)	3 (0 to 5)	3 (0 to 8)	

of developmental delay, presence of status epilepticus before VNS, seizure frequency, and number of AEDs used before VNS between the two groups. Only prior resective epilepsy surgery showed a trend with patients who completed the survey having a higher rate of prior surgeries compared to patients who did not (31% vs 17%, p = 0.052). Also, the differences between patients who did and did not complete the survey were not significant for epilepsy classification (Table 3), duration of VNS therapy (Table 4), and stimulation parameters at the last VNS setting documented in EMR (Table 5).

3.3. Survey responses

For those patients who completed the survey, the average age at survey was 39 years (range: 8 to 70 years). The median duration of VNS therapy was 7 years (range: 0 to 16 years) with 36% (n = 33) being 10 or more years. The vast majority (92%) of the patients were still receiving VNS therapy. The median number of AEDs at the time of the survey was 3 (range: 0 to 8). Twenty-five (28%) patients had experienced a VNS complication. However, 72 (80%) considered the VNS implantation worthwhile.

3.4. Favorable outcomes

Among the 90 patients with surveys, 10 had insufficient information to compute the modified Engel class. Seizure frequency was missing for 7 patients from the survey, 2 from before VNS and 1 from both time points. For the remaining 80 patients, 16 (20%) had class I (seizure-free), 14 (18%) had class II (>90% SR), 24 (30%) had class III (50–90% SR), and 26 (33%) had class IV (<50% SR) outcomes. A favorable outcome, defined as more than 50% reduction in seizure frequency, was associated with a lower output current (≤2 mA: 73% vs >2 mA: 42%, p = 0.03, Table 5). The association of >50% SR and epilepsy classification showed a trend (p = 0.053, Table 3) with 88% of patients with temporal lobe epilepsy having the highest rate of favorable seizure outcomes while 38% of patients with multiple types had the lowest rate. The associations of >50% SR with age at survey, gender, race, age at epilepsy onset, age at VNS, duration between epilepsy onset and VNS implantation, presence of developmental delay, presence of status epilepticus before VNS, seizure frequency before VNS, number of AEDs used before VNS, and resective epilepsy surgery were not significant.

3.5. Psychosocial outcomes

Among the 90 patients, 43 patients were ≥18 years old at VNS implantation without developmental delay in whom psychosocial outcomes were further analyzed. There was a decrease in the number of patients driving (31% vs 14%, p = 0.052) and working (44% vs 35%, p = 0.285) and an increase in the number of patients using antidepressant medication (14% vs 28%, p = 0.057) at the time of survey compared to before VNS.

3.6. Psychosocial metrics and favorable seizure outcomes

In the subset of 43 patients who were adults at the time of VNS implantation and had no developmental delays, 35 had modified Engel

Table 3
Survey and seizure outcomes by epilepsy classification.

Epilepsy classification	No survey (N = 62) N (%)	Survey completed (N = 90) N (%)	Favorable outcome (>50% SR) N (%)[a]
Idiopathic generalized	3 (5%)	5 (6%)	3 (75%)
Symptomatic generalized	10 (16%)	18 (20%)	10 (59%)
Temporal partial	17 (27%)	19 (21%)	15 (88%)
Extratemporal partial	22 (35%)	35 (39%)	21 (72%)
Multiple types	10 (16%)	13 (14%)	5 (38%)
p-Values	0.888		0.053

[a] Percentage of surveyed patients with seizure information (IG: n = 4, SG: n = 17, TP: n = 17, ETP: n = 29, and multiple types: n = 13).

Table 4
Seizure outcomes in surveyed patients by duration of VNS therapy (follow-up time since VNS implantation).

Duration of VNS therapy	All eligible patients N (%)	All surveyed patients N (%)[a]	Favorable outcome (>50% SR) N (%)[b]
0–4 years	43 (28%)	28 (65%)	17 (74%)
5–9 years	49 (32%)	29 (59%)	19 (68%)
10–14 years	36 (23%)	22 (61%)	11 (58%)
15+ years	24 (16%)	11 (46%)	7 (70%)
p-Values	NA	0.484	0.739

[a] Percentage of all eligible patients.
[b] Percentage of surveyed patients with seizure information (0–4 years: n = 23, 5–9 years: n = 28, 10–14 years: n = 19, and 15+ years: n = 10).

Table 5
Last VNS settings for stimulation parameters.

Stimulation parameters at last VNS setting		All eligible patients N (%)	All surveyed patients N (%)[a]	p-Values	Favorable outcome (>50% SR) N (%)[b]	p-Values
Output current (OC)	>2 mA	32 (21%)	16 (50%)	0.232	6 (42%)	0.03
	≤2 mA	120 (79%)	74 (62%)		48 (73%)	
Rapid cycling (RC)	>25%	22 (14%)	14 (64%)	0.648	6 (50%)	0.16
	≤25%	130 (86%)	76 (59%)		48 (71%)	

[a] Percentage of all eligible patients.
[b] Percentage of surveyed patients with seizure information (OC > 2: n = 14 and OC ≤ 2: n = 66; RC > 25: n = 12 and RC ≤ 25: n = 68).

scores computed with 21 (60%) having >50% SR. Patients with >50% SR were taking significantly fewer AEDs at the time of survey compared to patients with unfavorable outcomes (median: 3 vs 4, p = 0.045, Table 6). The associations of >50% SR with the psychosocial outcomes of driving, employment, and antidepressant use were not significant (Table 6). Overall, 77% of this subset said VNS was worthwhile, and this was not associated with >50% SR.

4. Discussion

This is the first study assessing the long-term impact of VNS therapy over more than 15 years for epilepsy, to our knowledge, on seizure outcomes and on selected psychosocial metrics. Our findings reveal that adjunct VNS therapy leads to >50% SR in 68% and seizure freedom in 20% of patients. In the earlier studies, shorter-term seizure outcomes seemed to improve with time on VNS therapy [3,17,18]. The enduring effect of any therapy could be determined by assessment of long-term outcomes. Seizure reduction of >50% appeared to have a stable effect sustained for up to 15 years in the surveyed patients in our study who had severe refractory epilepsies, in accordance with another study [8].

We assessed seizure outcomes in relation to epilepsy classification (Table 3) and observed that 88% of patients with temporal lobe epilepsy achieved >50% SR. Similar findings were noted by another study [5] and had contributed to the initial FDA approval of VNS for partial epilepsy. Rates of >50% SR with idiopathic generalized (75%) and extratemporal partial (72%) epilepsies that are usually associated with generalized tonic–clonic seizures were higher than that for symptomatic generalized epilepsy (59%) in accordance with other studies [5,19]. This seems logical, as symptomatic generalized epilepsies are known be characterized by multiple seizure types which are often drug-resistant.

During the course of VNS parameter settings, the output current was optimized or duty cycles were adjusted to the tolerance level in all patients. Only 18% of patients (16/90) had an output current >2 mA, and 16% (14/90) had rapid cycling parameters. Although some prior studies with shorter follow-up periods [2,20] indicated that high stimulation lead to better SR and one study by Heck et al. [15] showed a higher intensity current (>2 mA) did not provide any additional benefit, our findings demonstrated that a current ≤2 mA was significantly associated with >50% SR (p = 0.03). The XE5 study [21] revealed SR in a subgroup of patients with increased duty cycle, whereas another study failed to observe the same [17]. We observed that those without rapid cycling settings were associated with a higher >50% SR rate, although this difference was not statistically significant. This was of interest for the AAN subcommittee [22] as well, which, in 2013, could not conclusively determine any ideal VNS settings effective for SR. There was no significant difference in VNS complication per survey response when the settings had a high output current or rapid cycling.

In our patient cohort with severe epilepsies, AEDs were usually adjusted. In a 2002 study by Labar [23], the continuation of AEDs during the initial 12 months of VNS therapy was commonly noted with no worsening of seizures with AED reduction. In the patients we surveyed, there was an increase in the number of AEDs at the time of survey compared to before VNS implantation (3.4 ± 1.5 vs 3.0 ± 1.0, p = 0.027). Overall, the beneficial effects in SR might be attributable to the complementary effect of VNS and AEDs together.

Developmental delay was noted in almost half of our patients (44/90), and resective surgery was performed in almost a third of our patients (28/90) prior to VNS implantation. The presence of developmental delay or prior failed epilepsy surgery did not affect the seizure outcome of VNS therapy as noted in another study [24] as well.

In our small sample size of patients without developmental delay, we found that 31% drove before VNS implantation, and 14% drove at the time of survey. Vagus nerve stimulation did not favorably affect driving status unlike resective epilepsy surgery [25] that we documented in our previous paper [12]. This is most likely due to less favorable post-VNS seizure-free outcomes compared to resective surgery.

Our findings show that there was a decrease in full-time employment status from before VNS implantation to after at the time of survey. This could be due to a relative aging of the surveyed patients with the passage of time, along with the ongoing seizures due to intractability of epilepsy.

Depression as a psychiatric comorbidity is well known in patients with intractable epilepsy. Vagus nerve stimulation has also been FDA approved as a treatment for severe, recurrent depression since 2005 and shown to be effective in a substantial minority of patients with refractory depressive disorders for up to one [26] or 2 years [27]. In our study, we found that when compared to before VNS initiation, almost double the patients were being treated with antidepressants at the

Table 6
Comparison of psychosocial outcomes by seizure outcomes in patients ≥18 years of age at VNS implantation without developmental delay.

Variable	Response	Favorable (>50% SR) (N = 21)	Unfavorable (<50% SR) (N = 14)	p-Value
Number of AEDs at survey	Mean ± S.D.	3.1 ± 1.6	4.1 ± 1.6	0.045
	Median (range)	3 (1 to 7)	4 (2 to 8)	
Driving status before VNS	Yes	9 (45%)	3 (21%)	0.157
	No	11 (55%)	11 (79%)	
Driving status at survey	Yes	4 (19%)	1 (7%)	0.445
	No, due to seizures	14 (67%)	12 (86%)	
	No, due to other reasons	3 (14%)	1 (7%)	
Employment status before VNS	Full-time	6 (29%)	3 (21%)	0.435
	Part-time	6 (29%)	2 (14%)	
	Not employed	9 (43%)	9 (64%)	
Employment status at survey	Full-time	3 (14%)	1 (7%)	0.666
	Part-time	6 (29%)	3 (21%)	
	Not employed	12 (57%)	10 (71%)	
Use of antidepressants before VNS	Yes	3 (14%)	1 (7%)	0.515
	No	18 (86%)	13 (93%)	
Use of antidepressants at survey	Yes	8 (38%)	2 (14%)	0.127
	No	13 (62%)	12 (86%)	
VNS worthwhile	Yes	17 (81%)	10 (71%)	0.610
	No	2 (10%)	3 (21%)	
	Unsure	2 (10%)	1 (7%)	

time of survey in spite of VNS therapy, possibly indicating continuing depressive symptoms due to refractory seizures or other ongoing comorbidities, depression as a side effect of AEDs, or better clinical recognition of depression when compared to that in the past.

Overall, 81% of the patients with VNS for intractable epilepsy thought it was worthwhile to have the therapy irrespective of the favorable (>50% SR) or unfavorable seizure and psychosocial outcomes. Much of this could be due to the very intractable nature of epilepsy in these patients who perhaps express contentment with relative improvement in their seizure frequency.

There are some limitations with this study. The survey response rate was 59%; nonetheless, we had similar rates in our earlier study [12]. Even though patients who did and did not complete the surveys appeared to be comparable on the reported patient characteristics, there is a possibility that there may be other unmeasured factors that differ between these two groups. A sensitivity analysis on the response of patients with >50% SR, which was observed to be 68% in this study, shows that the rate would range from 36%, if all the nonsurveyed patients did not have >50% SR, to 82%, if they all did. A second limitation of the study is the small sample sizes for some of the comparisons, especially for the psychosocial metrics in the adult population without developmental delays. The reduced sample size affects the power of the statistical tests to find clinically meaningful differences. However, information about these metrics in patients with epilepsy on VNS therapy is currently not available in the literature and hence may be valuable to patients and their health care providers. Another potential limitation of this study is responder bias. In this study, the data collection was performed by surveying the patients or their caregivers, with the possibility that the responders may not have been candid with their phone responses. During the phone surveys, to lower this potential bias, the responders were assured that their responses would be kept confidential, would be reported in an aggregate manner with no individual identification, and would not affect their medical care. Cross-validation of information with that available on EMR was done to minimize recall bias. Furthermore, retrospective study design has its own limitations, and does not include a control group. Nevertheless, considering the heterogeneous cohort with such difficult refractory epilepsies who are not surgical candidates or who did not benefit from epilepsy surgery, this study effectively demonstrates long-term outcomes on seizure and the psychosocial metrics in patients with epilepsy on VNS therapy.

5. Conclusion

This study shows that VNS is a well-tolerated long-term adjunctive therapy for epilepsy, associated with >50% seizure reduction in two-thirds of the patients and seizure freedom in one-fifth of the patients. This is the first study to demonstrate that, although there is no statistical difference in the psychosocial metrics before and after VNS implantation for intractable epilepsy irrespective of seizure outcomes, the great majority of patients express satisfaction with VNS therapy. Much of this could be due to the very intractable nature of challenging epilepsies in these patients who perhaps express satisfaction with relative seizure control. Overall, VNS seems to provide meaningful long-term improvement in outcomes when used as an adjunctive therapy for intractable epilepsies.

Financial support

There are no financial disclosures.

Acknowledgments

This work was performed at the Henry Ford Comprehensive Epilepsy Program, MI. The authors are very thankful to all the dedicated epileptologists — Drs. Basel Assaad, Gregory L. Barkley, David E. Burdette, Jules E.C. Constantinou, Shailaja Gaddam, Madhuri L. Koganti, Naznin A. Mahmood, Amit Ray, Lori A. Schuh, Robert T. Simkins, Brien J. Smith, and Andrew J. Zillgitt; and epilepsy surgeons — Drs. Kost Elisevich and Ellen Air who used their expertise in performing the procedures and providing care to our patients. We appreciate the help from the Department of Public Health Sciences for the public search database.

Conflicts of interest

None of the authors has any conflict of interest to disclose. 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.

References

[1] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342(5):314–9.
[2] Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51:48–55.
[3] Spanaki MV, Allen LS, Mueller WM, Morris III GL. Vagus nerve stimulation therapy: 5-year or greater outcome at a university-based epilepsy center. Seizure 2004;13(8):587–90.
[4] Ryzí M, Brázdil M, Novák Z, Chrastina J, Ošlejšková H, Rektor I, et al. Long-term vagus nerve stimulation in children with focal epilepsy. Acta Neurol Scand 2013;127(5):316–22.
[5] Englot DJ, Chang EF, Auguste KI. Efficacy of vagus nerve stimulation for epilepsy by patient age, epilepsy duration, and seizure type. Neurosurg Clin N Am 2011;22(4):443–8.
[6] García-Navarrete E, Torres CV, Gallego I, Navas M, Pastor J, Sola RG. Long-term results of vagal nerve stimulation for adults with medication-resistant epilepsy who have been on unchanged antiepileptic medication. Seizure 2013;22(1):9–13.
[7] Yu C, Ramgopal S, Libenson M, Abdelmoumen I, Powell C, Remy K, et al. Outcomes of vagal nerve stimulation in a pediatric population: a single center experience. Seizure 2014;23(2):105–11.
[8] Elliott RE, Morsi A, Tanweer O, Grobelny B, Geller E, Carlson C, et al. Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years. Epilepsy Behav 2011;20:478–83.
[9] Elliott RE, Rodgers SD, Bassani L, Morsi A, Geller EB, Carlson C, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. J Neurosurg Pediatr 2011;7(5):491–500.
[10] Klinkenberg S, Van den Bosch CN, Majoie HJ, Aalbers MW, Leenen L, Hendriksen J, et al. Behavioural and cognitive effects during vagus nerve stimulation in children with intractable epilepsy — a randomized controlled trial. Eur J Paediatr Neurol 2013;17(1):82–90.
[11] Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 2000;42(2 – 3):203–10.
[12] Wasade VS, Elisevich K, Tahir R, Smith B, Schultz L, Schwalb J, et al. Long-term seizure and psychosocial outcomes after resective surgery for intractable epilepsy. Epilepsy Behav 2015;43:122–7.
[13] Dupont S, Tanguy ML, Clemenceau S, Adam C, Hazemann P, Baulac M. Long-term prognosis and psychosocial outcomes after surgery for MTLE. Epilepsia 2006;47(12):2115–24.
[14] Tecoma ES, Iragui VJ. Vagal nerve stimulation use and effect in epilepsy: what have we learned? Epilepsy Behav 2006;8:127–36.
[15] Heck C, Helmers SL, DeGiorgio CM. Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. Neurology 2002;59(6, Suppl. 4):S31–7.
[16] Wheeler M, De Herdt V, Vonck K, Gilbert K, Manem S, Mackenzie T, et al. Efficacy of vagus nerve stimulation for refractory epilepsy among patient subgroups: a re-analysis using the Engel classification. Seizure 2011;20(4):331–5.
[17] Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. Seizure 2004;13:392–8.
[18] Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bingaman WE. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. Seizure 2006;15(7):491–503.
[19] Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, et al. Lennox–Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009;8:82–93.
[20] Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia 1994;35:616–26.
[21] DeGiorgio CM, Thompson J, Lewis P, Arrambide S, Naritoku D, Handforth A, et al. Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. Epilepsia 2001;42(8):1017–20.
[22] Morris GL, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013;81(16):1453–9.
[23] Labar DR. Antiepileptic drug use during the first 12 months of vagus nerve stimulation therapy: a registry study. Neurology 2002;59(6 Suppl. 4):S38–43.

[24] Elliott RE, Morsi A, Geller EB, Carlson CC, Devinsky O, Doyle WK. Impact of failed intracranial epilepsy surgery on the effectiveness of subsequent vagus nerve stimulation. Neurosurgery 2011;69(6):1210–7.
[25] Jones JE, Blocher JB, Jackson DC. Life outcomes of anterior temporal lobectomy: serial long-term follow-up evaluations. Neurosurgery 2013;73(6):1018–25.
[26] Cristancho P, Cristancho MA, Baltuch GH, Thase ME, O'Reardon JP. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. J Clin Psychiatry 2011; 72(10):1376–82.
[27] Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 2005;66(9):1097–104.