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Effect of Long-Term Treatment with Vagus Nerve Stimulation on Mood and Quality of Life in Korean Patients with Drug-Resistant Epilepsy

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Background and Purpose This study aimed to determine the long-term effects of vagus nerve stimulation (VNS) treatment on suicidality, mood-related symptoms, and quality of life (QOL) in patients with drug-resistant epilepsy (DRE). We also investigated the relationships among these main effects, clinical characteristics, and VNS parameters.

Methods Among 35 epilepsy patients who underwent VNS implantation consecutively in our epilepsy center, 25 patients were recruited to this study for assessing the effects of VNS on suicidality, mood-related symptoms, and QOL. The differences in these variables between before and after VNS treatment were analyzed statistically using paired *t*-tests. Multiple linear regression analyses were also performed to determine how the patients' demographic and clinical characteristics influenced the variables that showed statistically significant changes after long-term VNS treatment.

Results After VNS, our patients showed significant improvements not only in the mean seizure frequency but also in suicidality, depression, and QOL. The reduction in depression was associated with the improvement in QOL and more-severe depression at baseline. The reduction in suicidality was associated with higher suicidality at baseline, smaller changes in depression, and less-severe depression at baseline. Improved QOL was associated with lower suicidality at baseline.

Conclusions This study found that VNS decreased the mean seizure frequency in patients with DRE, and also improved their depression, suicidality, and QOL. These results provide further evidence for therapeutic effect of VNS on psychological comorbidities of patients with DRE.

Key Words epilepsy, vagus nerve stimulation, suicidality, depression, quality of life.

INTRODUCTION

Approximately one-third of patients with epilepsy (PWE) are unresponsive to antiepileptic drugs (AEDs), which is called drug-resistant epilepsy (DRE).[1] Most PWE suffer not only from disabling seizures but also a wide range of psychological comorbidities such as depression, anxiety, and high suicidality, which influence their quality of life (QOL) and seizure control.[2,3] It has been reported that suicidality is higher in PWE than in the general population.[4-6] A recent large Korean study investigated clinical correlates for suicide among epilepsy patients,[7] and found that a high seizure frequency and the use of antidepressants were associated with higher suicidality. Our previous study revealed that seizure-related symptoms are related to both suicidality and depression.[8]

Vagus nerve stimulation (VNS) is one of treatment options for patients with DRE. VNS

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involves stimulating the vagus nerve with electrical impulses, which is safe and effective not only at decreasing or even preventing seizures in epilepsy, but also improving depressive symptoms in patients with DRE.[9] However, the effects of VNS treatment on mood-related symptoms and QOL in patients with DRE have varied between studies. Some previous VNS studies showed a trend toward improvements in depression in epilepsy patients with a comorbid major depressive disorder,[10,11] and a significant improvement in depression after a 6-month follow-up.[12] In contrast, other VNS studies found no significant changes in depression, whereas significant improvements were observed on anxiety scales or QOL after VNS implantation.[13,14] While many studies have investigated the QOL in epilepsy patients who underwent resective surgery,[15-18] only a few studies have evaluated QOL changes in patients receiving VNS treatment.[14,19-21] Two studies found significant improvements in QOL at follow-ups after 12 months in 19 patients[20] and 3−12 months in 56 patients.[14] A recent 2-year follow-up study of VNS outcomes in 5,554 patients found that QOL improved significantly more in responders (>50% decrease in seizure frequency) than in nonresponders.[21] However, no previous study has investigated the effect of VNS on suicidality.

More than 100,000 epilepsy patients worldwide had undergone VNS implantation as of June 2018.[22] In Korea, more than 930 domestic patients were using VNS to control their seizures up to 2018. Several studies in other countries have investigated the effects of VNS on mood-related symptoms and QOL. However, there has been no report on the long-term effects of VNS on suicidality, mood-related symptoms, and QOL between before and after VNS treatment in patients with DRE. The primary objective of the present study was to determine the long-term effects of VNS on suicidality, mood-related symptoms, and QOL in patients with DRE. We also analyzed how the effects of VNS treatment are related to clinical and VNS parameters.

METHODS

Patients

This prospective study was approved by the Samsung Medical Center (SMC) Institutional Review Board (2016-05-055), and written informed consent was provided by patients undergoing VNS treatment. Thirty-five patients with DRE were consecutively recruited from patients who were scheduled for VNS device implantation in the SMC between January 2016 and September 2018. Twenty-five patients who completed a set of questionnaires for mood-related symptoms, suicidality, and QOL at baseline and at follow-up were included in this study. All patients were asked to keep accurate seizure logs during the period between the baseline and follow-up assessments. Medication was stable in all patients throughout the study, as well as the 2-month period preceding the baseline assessments. All of the included patients underwent a careful presurgical evaluation that included long-term video-EEG monitoring and brain MRI. All of the patients had DRE, with at least one unprovoked seizure per month despite taking two or more AEDs. All patients exhibited complex partial seizures (CPSs) with or without secondarily generalized seizures. Patients were excluded if they had cognitive impairment that was sufficiently severe to interfere with their ability to provide informed consent or to participate in the study.

Study design

This study was designed to evaluate the long-term effects of VNS on seizure outcome, mood symptoms, suicidality, and QOL during VNS treatment from baseline to follow-up. Baseline assessments were applied 1 day before VNS device implantation. All of the assessments performed at baseline were repeated when current of each patient reached ≥1.5 mA at least 3 months after surgery.

Vagus nerve stimulation

The NeuroCybernetic Prosthesis stimulating electrode and stimulator manufactured by LivaNova (previously Cyberonics, Houston, TX, USA) was used for VNS therapy. The VNS device was implanted subcutaneously in the left chest and neck under general anesthesia, and the stimulator was switched on at 2−4 weeks after surgery when the surgical wounds were healed and showed no sign of infection. The initial stimulation started with an output current of 0.25 mA, a frequency of 30 Hz, a pulse width of 500 μs, and on/off cycles of 30 s/every 5 min. The output current was gradually increased over several weeks from 0.25 mA to ≥1.5 mA, depending on the individual tolerance and the seizure outcome. The output current was generally increased at each visit (i.e., every 2−4 weeks). Patients were supplied with a handheld VNS magnet that could be used to activate stimulation when they felt an aura, in order to prevent its progression to seizure. When a patient complained about an adverse event related to stimulation, the pulse width was reduced to 250 μs or the output current was temporarily reduced with or without also decreasing the signal on time to 21 or 25 s.

Neuropsychological assessments

Three sets of questionnaires were used to assess depressive symptoms [Korean version of Beck Depression Inventory-II (K-BDI-II)[23,24]], anxiety [Korean version of Beck Anxiety Inventory (K-BAI)[25,26]], and suicidality [Mini International Neuropsychiatric Interview Plus (MINI Plus) version 5.0.0[27]]. The

K-BDI-II is the most widely used questionnaire for detecting depression, and consists of 21 items. The severity of current depressive symptoms was divided into four categories: 0−13, normal to minimal depression; 14−19, mild depression; 20−28, moderate depression; and 29−63, severe depression. The K-BAI is a 21-item instrument for measuring the severity of anxiety symptoms.[25] The total K-BAI score ranges from 0 to 63, and was used to divide the severity of anxiety symptoms into four categories: 0−9, normal to minimal anxiety; 10−18, mild to moderate anxiety; 19−29, moderate to severe anxiety; and 30−63, severe anxiety. Suicidal ideation and behaviors were evaluated with the suicidality subscale of the MINI Plus.[28] The severity of current suicidality was estimated from the weighted sum of scores for six questions: 0, no; 1−5, low suicidality; 6−9, moderate suicidality; and ≥10, high suicidality.

Health-related QOL (HRQOL) was assessed using the Korean version of Patient-Weighted Quality of Life in Epilepsy Inventory-31 (K-QOLIE-31-P), a questionnaire with 38 items for measuring HRQOL in PWE.[29] The HRQOL scores range from 0 (worst possible QOL) to 100 (best possible QOL). The overall K-QOLIE-31-P score was obtained as the weighted average of multi-item test scores.

Seizure measurement

Seizure frequencies of aura, simple partial seizures, CPS, and secondarily generalized tonic−clonic seizures (2GTC) were assessed by analyzing the seizure diaries of patients during the full study period. For all patients, changes in the frequencies of different seizure types at the follow-up were analyzed by calculating the postsurgery percentage change in the mean seizure frequency relative to the baseline mean seizure frequency.

Statistical analysis

Paired *t*-tests were used to compare changes in all variables (seizure frequency, mood-related symptoms, suicidality, and QOL) after long-term VNS relative to their baseline values. Multiple linear regression analysis was used to identify the factors potentially associated with significant changes in depressive symptoms, suicidality, and QOL after VNS treatment. The dependent variables were changes in depressive symptoms, suicidality, and QOL. Independent variables included age, sex, scores on the K-BDI-II, MINI Plus, and K-QOLIE-31-P at baseline, epilepsy-related variables, and VNS-related variables. The epilepsy-related variables were age at the onset of seizures, duration of epilepsy, type of epilepsy and seizures, and existence of MRI lesions. The VNS-related variables were whether or not a VNS magnet was used, stimulation voltage, and duration of VNS treatment.

The associations of dependent variables with independent ones are presented as the mean and 95%-confidence-interval values of unstandardized linear regression coefficients. In addition, all significant associations were ranked according to the absolute values of their standardized effects, which were quantified by the standardized regression coefficients. The tests of statistical significance were two-tailed, and significance was defined by $p<0.05$. All analyses were performed with SPSS software (version 25.0, IBM Corp., Armonk, NY, USA).

RESULTS

The demographic and clinical characteristics of all patients are summarized in Table 1. Their age at VNS implantation was 30.4±9.5 years (mean±SD), and the follow-up duration was 13.7±5.5 months. The type of epilepsy was multifocal in 25 patients (24 bilateral and 1 hemispheric). Seventeen patients experienced adverse events, comprising hoarseness (*n*=9), cough (*n*=2), shortness of breath (*n*=1), and neck tingling pain (*n*=5), all of which subsequently lessened or disappeared.

Paired *t*-tests revealed significant changes in depressive symptoms, suicidality, and QOL after long-term VNS treatment. These improvements were independent of the effects on seizure frequency (16 seizure responders versus 9 seizure nonresponders, with seizure response defined as >50% decrease in seizure frequency). The results from paired *t*-tests of mood- and QOL-related scores are summarized in Table 2. Regarding changes in depressive symptoms (K-BDI-II scores), 10 patients with mild (*n*=3), moderate (*n*=3), or severe (*n*=4) depression improved to normal after VNS treatment.

Table 3 presents the estimated significant associations of each dependent variable with independent variables based on a simple linear regression analysis. This analysis revealed that 1) the change in depressive symptoms was affected by the K-BDI-II score at baseline and the change in QOL, 2) the change in suicidality was affected by the K-BDI-II score at baseline, the change in the K-BDI-II score, and suicidality at baseline, and 3) the change in QOL was affected only by the change in the K-BDI-II score.

The results of multiple regression analyses are presented in Table 4. The strongest predictor of a smaller change in depressive symptoms was a larger QOL change, with an importance of 64.5%, followed by a higher K-BDI-II score at baseline with an importance of 35.5% (explanatory power of 60.4%). The strongest predictor of a smaller change in suicidality was a higher suicidality score at baseline, with an importance of 91.3%, followed by a smaller change in the K-BDI-II score and a lower K-BDI-II score at baseline, with importances of 4.7% and 4.0%, respectively (explanatory power of 92.2%). The only predictor of a larger change in QOL was lower sui-

Table 1. Demographic and clinical characteristics of all patients

No.	Age (years)	Sex	Seizure onset age (years)	Epilepsy duration (years)	Seizure types	MRI lesion	Seizure frequency at VNS device implantation (months), aura/SPS/CPS/GTC	Seizure frequency at follow-up (months), aura/SPS/CPS/GTC	No. of AEDs	Duration of VNS at follow-up (months)	VNS stimulation parameters, OC (mA)/SF (Hz)/PW (ms)/SOFT (s-min)	EEG findings, ictal EEG	Previous epilepsy surgery
1	25	F	16	9	Aura, CPS	WNL	33.0/0.0/5.0/0.0	1.0/0.0/3.0/0.0	7	8	2.00/30/500/30-5	R or bilat. frontotemporal	No
2	23	M	8	15	Aura, CPS, 2GTC	WNL	3.0/0.0/2.0/2.0	1.0/0.0/1.0/1.0	3	12	2.00/30/500/30-5	Bilat. frontopolar	No
3	46	F	15	31	Aura, CPS, 2GTC	Tumor in L T	4.0/0.0/4.0/4.0	1.5/0.0/1.5/0.0	5	12	2.25/30/500/30-5	L, R frontotemporal	No
4	25	M	12	13	CPS, 2GTC	WNL	1.0/0.0/2.0/1.0	0.0/0.0/1.0/0.0	6	10	2.00/30/500/30-5	Bilat. frontotemporal	No
5	29	F	19	11	Aura, CPS, 2GTC	WNL	3.5/0.0/3.5/0.0	0.0/0.0/1.0/0.0	4	15	2.00/30/500/30-5	R, L temporo-occipital	No
6	35	F	3	33	Aura, CPS	HTL	0.0/0.0/10.0/0.0	0.0/0.0/3.0/0.0	4	13	2.00/30/500/30-5	Bilat. frontotemporal	Yes
7	21	M	16	5	Aura, CPS, 2GTC	WNL	0.0/0.0/6.0/0.0	5.0/0.0/2.5/0.0	3	9	2.00/30/500/30-5	L, R frontotemporal	No
8	21	M	4	17	Aura, CPS, 2GTC	WNL	4.0/0.0/4.0/0.0	2.0/0.0/0.0/0.0	4	14	2.00/30/500/30-5	L, R temporal	No
9	19	M	9	10	MSPS, PGTC	WNL	0.0/200.0/0.0/0.0	0.0/64.0/0.0/0.0	4	10	2.00/30/500/30-5	Bilat. frontocentral	No
10	38	M	1	37	CPS, 2GTC	WNL	0.0/0.0/10.0/2.0	0.0/0.0/1.0/0.0	5	21	1.50/30/500/30-5	R, bilat. frontal	No
11	34	F	17	17	Aura, CPS, 2GTC	HS in R	20.0/0.0/20.0/0.0	3.5/0.0/12.5/0.0	4	20	2.00/30/500/30-5	R, bilat. temporal	Yes
12	57	F	12	45	Aura, CPS	HSI in L O	3.5/0.0/3.5/0.0	0.0/0.0/1.5/0.0	5	7	1.50/30/500/30-5	L, R temporal	No
13	34	F	2	31	CPS	Pachygyria in R FC	0.0/0.0/2.0/0.0	0.0/0.0/1.0/0.0	3	17	2.00/30/500/30-5	L, R frontotemporal	No
14	37	F	2	34	Aura, CPS	HTL	30.0/0.0/15.0/0.0	30.0/0.0/15.0/0.0	5	14	1.50/30/500/30-5	Bilat. frontocentral	Yes
15	45	M	9	32	Aura, CPS, 2GTC	ENC in L FR	0.0/0.0/25.0/0.0	0.0/5.0/5.0/0.0	4	9	2.25/30/500/30-5	L, R frontal	No
16	28	F	5	22	Aura, MSPS, CPS, 2GTC	WNL	1.0/1.0/1.0/1.0	0.0/0.0/0.0/0.0	3	22	2.50/30/500/30-5	R, L frontotemporal	No
17	23	M	8	14	MSPS, CPS, 2GTC	WNL	0.0/1.0/8.0/1.0	0.0/1.0/4.0/0.0	4	14	1.75/30/500/30-5	Bilat. frontocentral	No
18	27	M	11	15	Aura, CPS, 2GTC	WNL	0.0/0.0/3.5/0.0	0.0/0.0/2.0/0.0	5	13	1.75/30/500/30-5	L, bilat. frontotemporal	No
19	26	M	17	8	CPS, 2GTC	WNL	0.0/0.0/2.0/2.0	0.0/0.0/1.0/0.0	6	9	2.00/30/500/30-5	L, bilat. frontotemporal	No
20	32	F	1	30	Aura, CPS	WNL	3.5/0.0/10.0/0.0	0.0/0.0/7.0/0.0	7	32	2.50/30/500/30-5	Bilat. nonlocalized	No
21	22	F	5	16	Aura, CPS, 2GTC	WNL	6.0/0.0/6.0/1.0	0.0/2.0/0.0/0.0	5	11	1.75/30/500/30-5	R temporal	Yes
22	41	M	31	9	Aura, MSPS	Multiple CL	2.0/2.0/0.0/0.0	0.0/0.0/0.0/0.0	3	13	2.00/30/500/30-5	L frontocentral	No
23	20	F	12	7	CPS, 2GTC	Heterotopia	0.0/0.0/10.0/0.0	0.0/0.0/9.0/0.0	3	14	2.75/30/500/30-5	R, L frontotemporal	No
24	26	M	2	23	CPS, 2GTC	WNL	0.0/0.0/15.0/2.0	0.0/0.0/9.0/0.0	3	9	2.00/30/500/30-5	Bilat. frontal	No
25	25	F	13	11	CPS	HS in L	0.0/0.0/2.5/0.0	0.0/0.0/1.0/0.0	5	14	2.00/30/500/30-5	L, R frontotemporal	No
Mean±SD	30.4±9.5		10.0±7.0	19.8±11.2					4.4±1.2	13.7±5.5			

AEDs: antiepileptic drugs, bilat: bilateral, CL: calcified lesions, CPS: complex partial seizure, ENC: encephalomalacia, FR: frontal, FC: frontocentral, F: female, GTC: generalized tonic–clonic seizure, HS: hippocampal sclerosis, HSI: high signal intensity, HTL: hypothalamic lesion, L: left, M: male, MSPS: motor SPS, O: occipital, OC: output current, PGTC: primary GTC, PW: pulse width, R: right, SF: signal frequency, SOFT: signal on/off times, SPS: simple partial seizure, T: temporal, VNS: vagus nerve stimulation, WNL: within normal limit, 2GTC: secondary GTC.

cidality at baseline (explanatory power of 44.8%).

After long-term VNS treatment, the number of seizures per month was remarkably reduced in aura (from 8.18 to 2.79, p=0.059), CPS (from 7.39 to 3.57, p<0.001), and 2GTC (from 1.78 to 0.11, p=0.006). The reductions in seizure frequency in aura, CPS, and 2GTC were 65.9%, 51.8%, and 93.8%, respectively. Seven of 14 patients who used a VNS magnet found that this magnet prevented seizure progression.

Table 2. Comparison of mood, suicidality, and quality of life scores before and after vagus nerve stimulation treatment

	Baseline	Follow-up	*p*
Mood-related questionnaires			
K-BDI-II score	21.2±12.3	14.4±10.9	0.006*
K-BAI score	12.4±3.4	10.6±10.6	0.278
MINI Plus score	6.0±10.7	1.6±3.6	0.030*
K-QOLIE-31-P score	58.8±14.2	66.4±15.4	0.017*

Data are mean±SD values.
*p<0.05.
K-BAI: Korean version of the Beck Anxiety Inventory, K-BDI-II: Korean version of Beck Depression Inventory-II, K-QOLIE-31-P: Korean version of Patient-Weighted Quality of Life in Epilepsy Inventory-31, MINI Plus: Mini International Neuropsychiatric Interview Plus.

DISCUSSION

This prospective study has provided further evidence of long-term VNS treatment being associated with improvements in depressive symptoms, suicidality, and QOL in patients with DRE. Furthermore, significant relationships were found among mood-related symptoms, suicidality, and QOL.

The depressive symptoms in our patients reduced significantly after VNS treatment, with the K-BDI-II score decreasing from 21.2±12.3 to 14.4±10.9 (p=0.006). About 84% of our patients showed reductions in depressive symptoms af-

Table 3. Results from simple linear regression analyses of predictive factors associated with changes in depressive symptoms, suicidality, and QOL

Dependent variable	Predictive factor	Standardized coefficient (β)	*p*	*t*	R^2
Change in depressive symptoms	K-BDI-II score at baseline	-0.588	0.002*	-3.491	0.346
	Change in QOL	-0.691	<0.001*	-4.582	0.477
	Suicidality at baseline	-0.490	0.013	-2.696	0.240
	Change in suicidality	0.565	0.003	3.283	0.319
	Duration of VNS treatment	-0.457	0.022	-2.462	0.209
Change in suicidality	K-BDI-II score at baseline	-0.427	0.033*	-2.264	0.182
	Change in K-BDI-II score	0.565	0.003*	3.283	0.319
	Suicidality at baseline	-0.944	<0.001*	-13.705	0.891
	Duration of VNS treatment	-0.457	0.022	-2.462	0.209
	QOL at baseline	0.504	0.010	2.799	0.254
	Change in QOL	-0.592	0.002	-3.520	0.350
Change in QOL	Suicidality at baseline	-0.691	<0.001*	-4.582	0.477
	Change in suicidality	-0.592	0.002	-3.520	0.350
	MRI lesion at baseline	-0.452	0.023	-2.428	0.204
	Change in K-BDI-II score	-0.691	<0.001	-4.582	0.477
	QOL at baseline	-0.437	0.029	-2.330	0.192

*Statistically significant at p<0.05 after adjusting for the effects of the reduction in seizure frequency (aura, complex partial seizure, and secondarily generalized tonic–clonic seizures) on the improvements in depressive symptoms, suicidality, and QOL after VNS treatment.
K-BDI-II: Korean version of Beck Depression Inventory-II, QOL: quality of life, VNS: vagus nerve stimulation.

Table 4. Results from multiple regression analyses of predictors associated with improvement in depressive symptoms, suicidality, and QOL

Dependent variable	Predictor	Standardized coefficient (β)	Relative importance (%)	*p*	R^2
Change in depressive symptoms	Change in QOL	-0.446	64.5	<0.001*	0.604
	K-BDI-II score at baseline	-0.398	35.5	0.005*	
Change in suicidality	Suicidality at baseline	-0.850	91.3	<0.001*	0.922
	Change in K-BDI-II score	0.194	4.7	0.005*	
	K-BDI-II score at baseline	0.169	4.0	0.008*	
Change in QOL	Suicidality at the baseline	-0.919	100.0	<0.001*	0.448

*Statistically significant at p<0.05 using a multiple regression analysis after adjusting for the effects of the reduction in seizure frequency (aura, complex partial seizure, and secondarily generalized tonic–clonic seizures) on the improvements in depressive symptoms, suicidality, and QOL after vagus nerve stimulation treatment.
K-BDI-II: Korean version of Beck Depression Inventory-II, QOL: quality of life.

ter VNS device implantation. At the baseline assessment of depression, 18 patients showed mild (n=4), moderate (n=4), or severe (n=10) depression. While evidence has been accumulating on the therapeutic effect of VNS in patients with treatment-resistant depression,[29-35] the positive effect of VNS on mood in patients with DRE has been controversial. A study of 28 patients with DRE found no improvement in depression as measured by the BDI during a 6-month follow-up of VNS treatment.[13] A randomized controlled study of 112 patients undergoing 12 months of VNS therapy found improvement in QOL but no significant improvement in depression.[14] Conversely, three studies have found that VNS can exert antidepressive effects.[10-12]

Several hypotheses have been proposed for the mechanism underlying how VNS can change mood. One of them is the influence of VNS on neurotransmitters, which are involved in mood regulation (norepinephrine and serotonin).[10,36,37] Another one is the changes in metabolic activity of limbic structures that are closely related to mood.[10,37] As other factors, medication and improved seizure control may have contributed to the improvement in depressive symptoms. The present study found that depressive symptoms were reduced not only in seizure responders but also in seizure nonresponders. In addition, even after controlling for the seizure-related variables, our multiple regression results showed that changes in QOL and K-BDI-II scores at baseline were predictive of an improvement in depressive symptoms. There were no changes in AEDs in any of the patients throughout the study, and so antidepressive effects of medications and seizure controls can be excluded as a predictive factor for the finding of improved depression.

It is difficult to ascertain the direct effect of QOL changes on improving depressive symptoms from our study. However, the correlation between depressive symptoms and QOL might not only be related to these two factors, but also to various other mediating factors such as seizure frequency, adverse effects of AEDs, physical/cognitive functioning, and history of psychiatric comorbidity.[38,39]

We further found that reduced suicidality was significantly associated with higher suicidality at baseline, smaller changes in depressive symptoms, and lower K-BDI-II scores at baseline. The rate of seizures, psychiatric comorbidity, history of suicide attempts, and depression appear to play important roles in increasing suicide risk. In addition, AEDs (especially those with a GABAergic mechanism of action) appear to increase the presence of suicidal ideation at the beginning of treatment. However, we found that the reduction in suicidality was associated not only with the status of seizure activity but also with the status of AEDs. A 5-year observational study of patients with DRE showed that adjunctive VNS treatment has significant benefits for both suicidality and depression.[36]

The relationships among epilepsy, suicidality, and mood-related symptoms are multifactorial and bidirectional.[40] There have been conflicting interpretations about their relationships. In early investigations it was considered that epilepsy patients who take multiple AEDs for a long time and those who have social stigma or mood-related symptoms have a higher risk of suicide.[41] One Swedish study found that psychiatric disorders are associated with an increased suicide risk in PWE,[42] whereas another study found an increased risk of suicide in the absence of psychiatric disorders.[43] A recent population-based retrospective study[44] from the United Kingdom suggested that the biological or genetic makeup (or both) of PWE puts them at risk of suicidality. A study of adolescents who had been referred for psychiatric assessments found that the self-reported QOL significantly mediated the relationship between emotion and suicide risk.[45] Together the above results imply that changes in suicidality and depressive symptoms are not simply the result of a change in QOL or VNS treatment in PWE, instead seeming to indicate a role of the underlying mechanisms of suicidality and epileptic behavior.

The present study found that a significant improvement in QOL was only associated with suicidality at baseline. A previous study of 702 PWE found that the strongest predictor of the overall Quality of Life in Epilepsy Inventory-10 (QOLIE-10) score was adverse effects of AEDs (as measured using the Korean version of the Liverpool Adverse Event Profile score), seizure control, Generalized Anxiety Disorder-7 (GAD-7) score, and household income.[46] Depression and seizure control have been found to be major predictors of QOL in many studies.[46-52] Similar to our results, a randomized controlled VNS study[14] demonstrated that the improvement in QOL and reduction in seizure frequency increased gradually over time, peaking at the 12-month follow-up, and with no statistically significant changes at 3-, 6-, and 9-month follow-ups. Those authors suggested that the VNS-induced improvement in QOL reflects the combination of modest changes in multiple factors rather than a single determinant. Two other studies[12,20] found a positive effect of VNS on QOL, but they found no significant correlation with changes in the seizure frequency. One study found that a shorter time to implant the VNS device was a predictor of improvement in QOL, but this result did not exclude the effect of changes in seizure frequency.[21] Another study using a correlation analysis rather than a regression analysis also found improvement in QOL after VNS treatment, with this change not being correlated with the change in seizure frequency.[20] The present study similarly found no significant relationship between QOL and seizure activity. Therefore, we can suggest that the improvement in QOL in the present study was affected by interactions among

different effects of VNS, including improvements in depressive symptoms and suicidality.

Regarding the effect of VNS on seizure reduction in the present study, the mean reductions in seizure frequencies in aura, CPS, and 2GTC were 65.9%, 51.8%, and 93.8%. A recent systematic review including 2,869 patients found that 49% of the patients responded to VNS therapy at 4 months after device implantation (>50% decrease in seizure frequency), with 5.1% of patients becoming seizure-free, while 63% of patients were responders at 24–48 months, with 8.2% achieving seizure freedom.[9] There are several previous reports on the seizure reduction efficacy being better for high-intensity VNS than low-intensity VNS.[53,54]

In conclusion, this study has confirmed that VNS can improve not only seizure control in patients with DRE but also their depressive symptoms, suicidality, and QOL. These findings provide further evidence for the adjunctive value of VNS treatment in managing psychological comorbidities in patients with DRE.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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