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Favorable combinations of antiseizure medication with vagus nerve stimulation to improve health-related quality of life in patients with epilepsy

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ABSTRACT

Background: Vagus nerve stimulation (VNS) is a non-pharmacological treatment of refractory epilepsy, which also has an antidepressive effect. The favorable combinations of VNS with specific mechanisms of action of antiseizure medication (ASM) on mood and health-related quality of life (HrQol) have not yet been studied. The objective was to identify favourable combinations of specific ASMs with VNS for the HrQoL and depression in refractory epilepsy.

Methods: We performed an observational study including patients with refractory epilepsy and an implanted VNS (N = 151). In the first 24 months after VNS implantation, all patients were on stable ASM therapy. We used the standardized questionnaires QOLIE10, EQVAS and EQ5D to evaluate HrQoL as well as the Beck Depression Inventory (BDI). Multiple regression analysis was performed to evaluate the synergistic combinations of ASM with VNS for HrQoL.

Results: At the year-two follow-up (N = 151, age 45.2 ± 17.0 years), significant improvement ($p < 0.05$) in BDI scores was found for combination of VNS with SV2A modulators (58.4 %) or AMPA antagonists (44.4 %). A significant increase of HrQoL by at least 30 % ($p < 0.05$) was measured for a combination of VNS with SV2A modulators (brivaracetam, levetiracetam) or slow sodium channel inhibitors (eslicarbazepine, lacosamide).

Conclusion: The results of our study suggests a favorable effect of the combination of SV2A modulators or slow sodium channel inhibitors with VNS on the HrQoL in comparison to other ASMs. Besides the possible synergistic effects on the seizure frequency, the amelioration of behavioral side effects of SV2A modulators by VNS is an important factor of HrQoL-improvement in these combinations.

1. Introduction

The prevalence of refractory epilepsy is within the range of 27–35 % and therefore requires increased medical attention [1]. Vagus nerve stimulation (VNS) is an established, effective procedure for the treatment of refractory epilepsy in addition to antiseizure medication (ASM) when resective surgery is not possible or is rejected by the patient [2]. Other options of neurostimulation include deep brain stimulation and

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASM, antiseizure medication; BDI, Beck Depression Inventory; CI, confidence interval; EASEE, Epicranial Application of Stimulation Electrodes for Epilepsy; EEG, electroencephalography; EQVAS, EuroQol Visual analogue scale; EQ5D, EuroQol-5-Dimensions Questionnaire; HrQoL, Health-related Quality of Life; MAINZ-EPIREG, Mainz Epilepsy Registry; QOLIE10, Quality of Life in Epilepsy-10; SD, standard deviation; SV2A, synaptic vesicle glycoprotein 2A; VNS, vagus nerve stimulation.

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responsive stimulation [3]. In addition, a new type of neurostimulation, direct cortical stimulation with the EASEE® device (Epicranial Application of Stimulation Electrodes for Epilepsy), was recently approved in Europe [4]. The response rate (at least 50 % reduction in seizure frequency) of implantable VNS varies from 45 to 65 % and increases in the long term [5–7].

The antidepressive effect of VNS is widely known as well as the influence of different antiseizure medications (ASM) on mood and the health-related quality of life (HrQoL) in epilepsy [3]. However, the effect of the combination of VNS with different mechanisms of action of ASM on mood and HrQoL in epilepsy have not been studied before. Identifying the favorable combination of VNS with some specific mechanisms of actions of ASMs in patients with refractory epilepsy could be an opportunity to improve the course of the disease and to improve the patients' HrQoL [8]. A recent study evaluated HrQoL in epilepsy patients without VNS and found that ASM side effects and depression are the main HrQoL determinants in this population [9]. The HrQoL in patients with polytherapy was by 20 % lower than in monotherapy. The use of VNS helps to avoid the drug burden. Taking into consideration this data, the search for favorable combinations of VNS and pharmacotherapy in order to reduce side effects and improve the mood would be the next logical step.

The aim of this study was to identify synergistic effects of specific ASMs in combination with VNS on HrQoL and depression in patients with epilepsy and to identify clinical variables improving HrQoL.

2. Methods

2.1. Study design and clinical evaluation

We performed an observational study in patients with refractory epilepsy who were implanted with VNS and remained on unchanged ASM during the first 24 months after the initiation of VNS. The implantation of the VNS-system was performed in the neurosurgical departments of three German university medical centers (Hannover, Mainz and Mannheim). After implantation, all study participants were evaluated in the neurological department of the University Medical Center in Mainz and participated in the Mainz Epilepsy Registry (MAINZ-EPIREG) [10]. The Registry is led by the Mainz Comprehensive Epilepsy and Sleep Medicine Center, which is part of the Department of Neurology of the University Medical Center of the Johannes-Gutenberg University, Mainz, Germany. The patients were motivated not to change ASM during the first years after VNS implantation, even if the result of VNS treatment did not correspond to their initial expectations. It is known that VNS therapy improves the seizure control even after years since the implantation and it was our argument to motivate the patients' patiency. In order to exclude the possibility of selection bias and to prove the generalizability of the results, we compared clinical parameters of patients excluded from the participation due to changes of ASM (approximately 30 %) with those who paticipated in the study. No significant differences in demographics, number of ASM or the seizure frequency at baseline were detected.

Data collection was performed before the implantation of VNS (baseline) and at the follow-up after two years. The following data was collected: demographics, epilepsy type, implanted VNS type, ASM, seizure frequency, depression and HrQol. In order to collect the information on ASM we used self-report questionnaires and compared this data with clinical documentation. Data concerning seizure freedom and responder rate was collected using standardized diaries. Seizure freedom was defined as the absence of epileptic seizures for a period of at least six months before the end of the study period. The definition of the responder rate refers to the monthly reduction of at least 50 % in seizure frequency in comparison to the time before implantation. The data were processed pseudonymously.

This study was approved by the Ethics committee of the Rhineland-Palatinate Chamber of Physicians and written informed consent was obtained from all participating patients prior to the start of the study. The study conforms with World Medical Association Declaration of Helsinki.

2.2. Evaluation of HrQoL and depression

We used standardized questionnaires including the Quality of Life in Epilepsy-10 (QOLIE10), the EuroQol Visual analogue scale (EQVAS) and the EuroQol-5-Dimensions Questionnaire (EQ5D) to evaluate HrQoL. The results of the individual questionnaires were analyzed for each ASMs and for substance groups (fast sodium channel inhibitors: lamotrigine, carbamazepine, oxcarbazepine; valproate; slow sodium channel inhibitors: eslicarbazepine, lacosamide; AMPA-antagonists: perampanel; GABAergic drugs: clobazam, pregabaline, topiramate, phenobarbital, valproate; calcium channel inhibitors: ethosuximid; topiramate, zonisamide; carbonic anhydrase inhibitors: topiramate, zonisamide). The questionnaire EQ5D is a validated tool to assess the subjective HrQoL of patients with epilepsy [11]. It reports the health status of the patients via 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 3 levels for each item (1 = no problems, 2 = moderate problems, 3 = severe problems) as well as via a visual analogue scale (EQVAS) with values from 0 ("worst conceivable health status") to 100 ("best conceivable health status"). We also used a validated disease-specific questionnaire, the QOLIE-10, to assess HrQoL in epilepsy, applied in its extended version QOLIE-10-P (version 2.0) and consisting of parts A-C with a total of 12 questions [12]. Part A asks about emotions and medication/disease-related limitations in daily life within the last four weeks; Part B refers to the assessment of quality of life in the last four weeks; in Part C, seven areas (energy, emotional state, daily activities, mental activity, effects of the medication, worries about seizures, overall quality of life) are ranked according to their subjective importance. A lower total score indicates a better HrQol.

Depression was evaluated by the Beck Depression Inventory (BDI, version 2), which assesses the presence of depression within the last two weeks via 21 statement groups such as "feelings of failure", "concentration difficulties", "loss of energy", "suicidal thoughts", etc. It uses values from 0 (the statement does not apply at all) to 3 (the statement applies completely). Depression within the BDI is categorized as "mild" (scores < 20), "moderate" (scores of 20 to 28) or "severe" (scores $>/= 29$) [13].

2.3. Statistics

Statistical analysis was performed using IBM SPSS Statistics Version 28.0 (IBM Corp., Armonk, NY, USA). Normal distributed data was proved by use of the Kolmogorov-Smirnov test and, additionally, by application of a *t*-test or analysis of variance. For non-normally distributed data, we applied the Kruskal-Wallis test (>two independent groups) or the Mann-Whitney *U* test (two independent groups). The data is presented by determining a mean value within a 95 % confidence interval (CI) and by calculating the standard deviation (SD). Statistical significance was determined using a p-value of < 0.05. Independent factors influencing the HrQoL were evaluated by applying multivariate regression analysis. We applied the R^2 method to estimate the variability accounted for by independent factors of HrQol.

3. Results

The study included 151 adult patients with a mean age of 45.2 years ± 15.3 years. In this cohort, 55.0 % of patients were female. The majority of patients suffered from a structural epilepsy (69. 5 %), followed by 29.1 % with an idiopathic generalized epilepsy and 1.3 % with an unknown type of epilepsy. The AspireSR® stimulation system from LivaNova, Inc. was implanted in 50.3 % of patients; SenTiva® in 37.1 %. Older VNS devices such as Demipulse® and VNS Therapy® Pulse 102

were used more rarely. Table 1 shows the demographic and clinical data. On average, patients took four ASMs in the period before implantation. At the follow-up after two years, a reduction in seizure frequency of at least 50 % was reported by 71 patients (47.0 %); seizure freedom was achieved by 11.9 % in total. No statistically significant differences in VNS parameters (output current, signal frequency, signal on-time and signal off-time) were found between different ASM groups.

At the two-year follow-up, the following improvements in mean scores of depression and HrQol measures were observed: 8.4 ± 17.1 on BDI, 14.6 ± 17.8 on QOLIE10, 0.12 ± 0.17 on EQ5D index and 11.9 ± 19.5 on EQVAS. Fig. 1 and Table 2 present the distribution of HrQol parameters and depression according to the substance groups and single ASMs. The BDI scores at baseline were generally higher than at the follow-up after two years showing a trend for a better mood under VNS in the entire study population. For SV2A modulators and AMPA antagonists, the level of depression was more prominent at baseline but did not reach statistically significant values in comparison to other substance groups. At the follow-up after two years, depression was significantly improved ($p < 0.05$) in these two substance groups (58.4 % in SV2A modulators and 44.4 % in AMPA antagonists) in comparison to baseline. The two years trends in the level of depression in other substance groups did not show statistically significant changes. According to the single substances, the highest BDI scores at baseline were registered for levetiracetam and perampanel. The improvement of depression after two years of VNS treatment was best in patients with brivaracetam, levetiracetam or perampanel (54.2–63.2 %, $p > 0.05$).

A general trend to HrQol-improvement on VNS-treatment was observed in the entire study population. However, the magnitude of HrQol-improvement was different depending on the combination of VNS with different ASMs. The combination of VNS with an ASM acting via slow sodium channel inhibition showed a significant increase in HrQol after two years as measured by QOLIE10 (48.7 %, $p < 0.05$), by EQ5D index score (33.9 %, $p < 0.05$) and by EQVAS (30.0 %, $p < 0.05$). Similarly, the combination of VNS with SV2A modulators led to significant HrQol-improvement on QOLIE10 (by 48.6 %, $p < 0.05$), in the EQ5D index score (by 31.1 %, $p < 0.05$) and on EQVAS (by 32.1 %, $p < 0.05$). From all ASMs analyzed in our study, brivaracetam, eslicarbazepine, lacosamide and levetiracetam showed significant improvement of HrQol by at least 30 % ($p < 0.05$) at the follow-up after two years (Table 2).

Table 3 summarizes the results of the regression analysis for the HrQol measures. Independent factors increasing HrQol were a lower severity depression measured by BDI and an improved effectiveness of treatment expressed by response rate. These clinical variables could explain 48 % of QOLIE10-values, 54 % of EQ5D index scores and 51 % of EQVAS values.

Table 1
Demographic and clinical data of patients with epilepsy and VNS.

	All patients n = 151	Idiopathic generalised epilepsy n = 44	Focal epilepsy n = 105	Unknown epilepsy type n = 2
Age [years]				
mean ± SD	45,2 ± 15,3	34,7 ± 11,8	49,8 ± 17,1	36,5 ± 0,7
Gender [n] (%)				
female	83 (55,0)	26 (59,1)	56 (53,3)	1 (50,0)
male	68 (45,0)	18 (40,9)	49 (46,7)	1 (50,0)
VNS type [n] (%)				
SenTiva®	56 (37,1)	17 (38,6)	38 (36,2)	1 (50,0)
AspireSR®	76 (50,3)	22 (50,0)	53 (50,5)	1 (50,0)
Demipulse®	6 (4,0)	3 (6,8)	3 (2,9)	0 (0)
VNS Therapy® Pulse 102	13 (8,6)	2 (4,5)	11 (10,5)	0 (0)
Previous ASM [n]				
mean ± SD	4,4 ± 2,9	4,2 ± 2,8	4,5 ± 3,0	2,0 ± 1,4
Response rate[1] after year 2 [n] (%)	71 (47,0)	23 (52,3)	47 (44,8)	1 (50,0)
Seizure freedom[2] after year 2 [n] (%)	18 (11,9)	6 (13,6)	11 (10,5)	1 (50,0)

Abbreviations: ASM, antiseizure medication; SD, standard deviation; VNS, vagus nerve stimulation.

[1] Response rate was defined as a reduction in seizure frequency of ≥ 50 % compared to baseline.

[2] Seizure freedom was defined as the absence of epileptic seizures for a period of at least six months before the end of the observation period.

4. Discussion

The role of different mechanisms of actions of ASMs in different types of epilepsy and their influence on HrQol is becoming a matter of increased interest in recent studies [14,15]. In refractory epilepsy, the effects of the combination of VNS with different ASMs and their influence on the HrQol is of special importance. Few recent studies have investigated the HrQol in epilepsy patients with VNS. The EQ5D, EQ-VAS and QOLIE10 are the most common tools for measuring HrQol in epilepsy and were also used in our study. In a retrospective study with 70 epilepsy patients from Valencia, the influence of VNS treatment on HrQol was assessed by means of QOLIE10: in the first year after VNS-implantation, approximately 93 % of patients reported an increase in HrQol. The mean improvement in QOLIE10 scores was 8.5 ± 7.2 [16]. A similar trend was detected in our study with a mean change in QOLIE10 scores of 14.6 ± 17.8 during the two-year follow-up. The response rate (≥50 % reduction in seizure frequency) was higher in the Spanish study (57.2 % vs 47.0 % in our patients), probably because further adjustments of ASMs were undertaken during the first year after VNS implantation. In our study, ASMs were kept unchanged during the first two years after implantation. According to various studies and *meta*-analyses, the response rate of implantable VNS varies from 45 % to 65 % and increases in the long term [5,17]. The effect on the seizure frequency in our study was within this range.

The influence of the combination of VNS with different types of ASMs on the HrQol in epilepsy has not been investigated until now. Therefore, our results concerning this specific question cannot be compared with other studies. The multiple regression analysis revealed that the most important factors influencing HrQol in the context of combination of VNS with different ASMs are the response rate (effectiveness) and the reduction of depression. These factors are already known as predictors of HrQol in epilepsy. For example, Chen et al. listed four negative predictive factors (depression, seizure frequency of at least once in three months, anxiety and adverse events of ASM) and three positive predictors (higher household income, male gender and social support) [18]. Depression is a frequent comorbidity in epilepsy [19,20]. Due to the neuroanatomical structures and neurotransmitters involved, a bidirectional relationship between the two disorders is suspected [21]. Since VNS is also approved for the treatment of depression, the advantage of VNS in epilepsy is the possibility not only to influence the seizures but also to treat the concomitant depression.

We found that two groups of ASMs with distinctive mechanisms of action show statistically significant improvement of HrQol in epilepsy when combined with VNS: SV2A modulators and slow inhibitors of sodium channels. According to our previous data, the combination of VNS and ASMs with these mechanisms of action has a synergistic effect on seizure frequency. As a possible pathophysiological explanation, the mutual potentiation in desynchronization of electroencephalographic (EEG) rhythms, which is known for VNS [22] and SV2A modulators [23–25] was discussed. As outlined above, the improvement of depression is an important factor influencing HrQol. The level of depression was higher at baseline in our patients treated with SV2A modulators. The initiation of additional VNS therapy in these patients helped to significantly improve depression. Therefore, the combination of VNS with SV2A modulators could be favorable not only because of

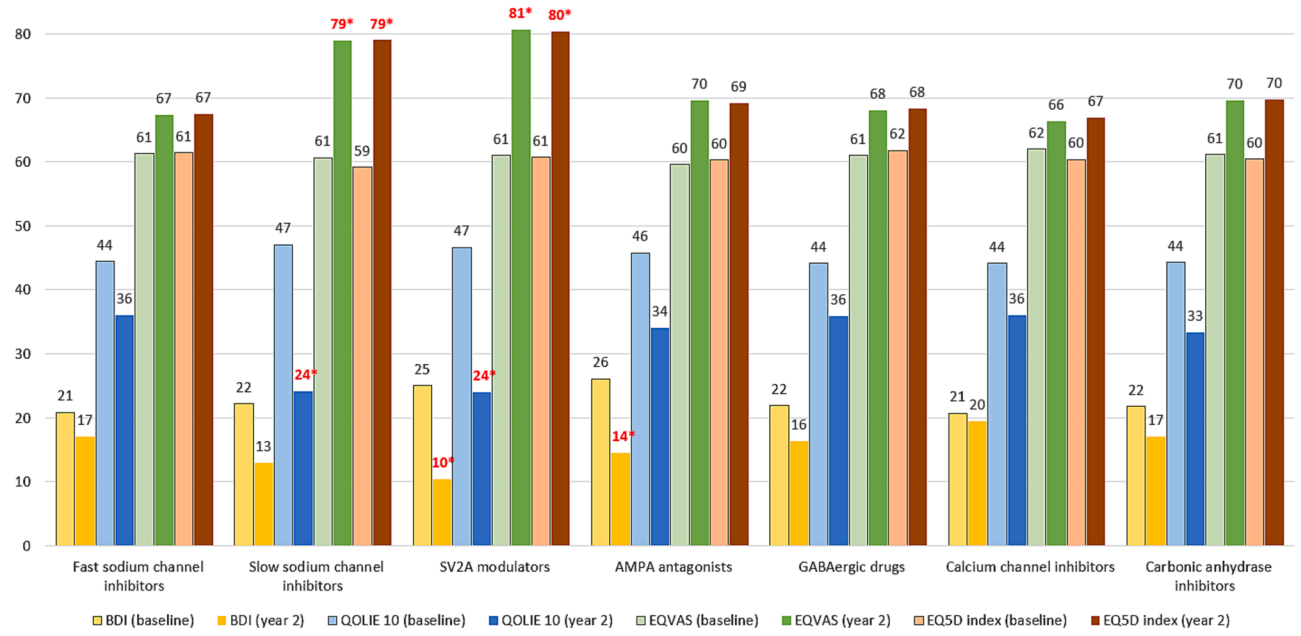

Fig. 1. Health-related quality of life data prior to VNS-implantation and at two-year follow-up, divided according to substance groups * Statistically significant difference at $p < 0.05$ in comparison to baseline (presented in red color). The values of the EQ5D index score were multiplied by factor 100 in order to optimize the graphical presentation. Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASM, antiseizure medication; BDI, Beck Depression Inventory (Version 2); EQVAS, EuroQol visual analogue scale; EQ5D, EuroQol-5-Dimensions Questionnaire; GABA, gamma-aminobutyric acid; QOLIE10, Quality of Life in Epilepsy-10; SD, standard deviation; SV2A, synaptic vesicle glycoprotein 2A; VNS, vagus nerve stimulation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Health-related quality of life data prior to VNS-implantation and at two-year follow-up, divided according to adjunctive ASMs.

	BDI ***baseline*** mean ± SD	**BDI** ***year two*** mean ± SD	**QOLIE10** ***baseline*** mean ± SD	**QOLIE10** ***year two*** mean ± SD	**EQVAS** ***baseline*** mean ± SD	**EQVAS** ***year two*** mean ± SD	**EQ5D index score** ***baseline*** mean ± SD	**EQ5D index score** ***year two*** mean ± SD
Adjunctive ASM								
Valproate	21.0 ± 11.6	15.4 ± 9.9	43.7 ± 8.8	36.3 ± 13.4	59.5 ± 9.1	66.3 ± 17.8	0.61 ± 0.09	0.68 ± 0.18
Lamotrigine	19.8 ± 12.4	17.5 ± 11.1	43.7 ± 8.3	35.4 ± 14.1	61.7 ± 10.6	68.4 ± 17.5	0.63 ± 0.10	0.69 ± 0.17
Lacosamide	22.5 ± 11.6	12.0 ± 8.3	47.0 ± 4.8	24.1 ± 15.2*	60.5 ± 8.6	78.5 ± 15.4*	0.59 ± 0.08	0.78 ± 0.15*
Levetiracetam	27.7 ± 11.2	10.2 ± 7.9*	46.7 ± 6.0	25.3 ± 15.1*	61.0 ± 10.1	78.3 ± 14.7*	0.60 ± 0.09	0.78 ± 0.14*
Brivaracetam	22.7 ± 10.2	10.4 ± 8.1*	46.6 ± 5.2	22.8 ± 12.5*	60.9 ± 9.1	82.4 ± 12.1*	0.62 ± 0.09	0.82 ± 0.12*
Carbamazepine	20.8 ± 10.2	15.6 ± 7.4	46.4 ± 6.5	38.2 ± 15.0	61.8 ± 9.5	68.2 ± 13.7	0.59 ± 0.08	0.67 ± 0.13
Eslicarbazepine	19.9 ± 10.1	14.0 ± 11.1	47.5 ± 4.6	22.1 ± 12.5*	59.8 ± 9.7	83.3 ± 11.9*	0.58 ± 0.07	0.84 ± 0.12*
Topiramate	22.8 ± 12.1	15.5 ± 10.0	44.9 ± 8.5	35.4 ± 14.2	59.5 ± 9.5	68.9 ± 14.2	0.60 ± 0.08	0.68 ± 0.13
Zonisamide	20.4 ± 13.5	19.3 ± 11.3	44.2 ± 8.2	33.8 ± 16.2	61.5 ± 10.9	67.9 ± 18.8	0.60 ± 0.09	0.69 ± 0.19
Perampanel	27.7 ± 10.6	14.0 ± 9.3*	45.2 ± 7.3	34.6 ± 15.0	59.0 ± 9.6	69.4 ± 16.9	0.61 ± 0.08	0.69 ± 0.16
Pregabalin	24.3 ± 11.0	19.5 ± 9.6	44.9 ± 5.5	35.3 ± 14.5	60.9 ± 9.2	69.5 ± 13.7	0.63 ± 0.05	0.69 ± 0.15
Oxcarbazepine	20.0 ± 14.3	16.9 ± 8.6	44.8 ± 10.0	38.7 ± 16.6	63.5 ± 7.1	60.0 ± 19.6	0.60 ± 0.11	0.59 ± 0.20
Clobazam	21.4 ± 11.1	16.9 ± 9.1	42.7 ± 8.2	36.1 ± 14.3	64.0 ± 8.9	67.1 ± 18.9	0.65 ± 0.09	0.67 ± 0.19
Ethosuximide	23.8 ± 12.5	19.2 ± 8.6	44.6 ± 10.4	43.0 ± 14.3	65.6 ± 11.6	61.7 ± 15.2	0.62 ± 0.10	0.63 ± 0.17
Phenobarbital	24.7 ± 15.1	16.1 ± 7.4	45.4 ± 6.1	36.9 ± 11.4	63.2 ± 10.1	68.6 ± 10.5	0.63 ± 0.05	0.69 ± 0.12

Abbreviations: ASM, antiseizure medication; BDI, Beck Depression Inventory (Version 2); EQVAS, EuroQol visual analogue scale; EQ5D, EuroQol-5-Dimensions Questionnaire; QOLIE10, Quality of Life in Epilepsy-10; SD, standard deviation; VNS, vagus nerve stimulation.
* Statistically significant difference at $p < 0.05$ in comparison to baseline.

synergistic effects on the effectiveness but also in order to ameliorate the behavioral side effects of SV2A modulators. It is important to remark that VNS therapy also significantly reduced the level of depression in combination with perampanel. However, the synergistic effect of this combination on the seizure frequency was not shown in our previous analysis and, therefore, no significant influence on HrQol was registered.

Our study has several limitations. First, we did not collect data from long-term follow-ups beyond two years. The evidence of our observational study is inferior to randomized controlled studies. However, no randomized controlled studies have been performed to investigate the effects of VNS in combination with different ASMs. The large ranges of BDI and EQ5D index score are due to high variability and due to the small numbers (<100) of patients in the subgroup analyzes. Some subgroups of ASMs were quite small, such as in case of oxcarbazepine, pregabalin, ethosuximide and phenobarbital. These ASMs should be addressed in larger populations. It is also important to stress that a number of ASMs were not present in our analysis (phenytoin, gabapentin, cannabidiol, fenfluramine and cenobamate). Consequently, no evidence of their combination with VNS could be provided.

5. Conclusion

The results of our study suggest a favorable effect of the combination

Table 3
Multiple regression analysis of health-related life quality two years after the VNS-implantation.

	EQVAS			EQ5D index score			QOLIE10		
	B	95 % CI	p-value	B	95 % CI	p-value	B	95 % CI	p-value
Age	−0.01	−0.11; 0.80	0.78	0.00	−0.00; 0.00	0.63	−0.03	−0.13; 0.08	0.59
Female gender	1.12	−1.85; 4.10	0.46	−0.01	−0.04; 0.02	0.58	−0.64	−3.92; 2.63	0.70
Epilepsy type[1]	2.27	−1.01; 5.55	0.17	0.03	−0.01; 0.06	0.12	−1.44	−5.06; 2.17	0.43
VNS type[2]	0.40	−1.44; 2.25	0.67	0.01	−0.01; 0.03	0.34	0.17	−1.87; 2.20	0.87
Previous ASM	−0.07	−0.64; 0.05	0.81	−0.00	−0.01; 0.00	0.50	0.28	−0.35; 0.91	0.39
Response rate[3]	10.16	6.30; 14.02	0.00	0.11	0.07; 0.15	0.00	−9.91	−14.17; −5.65	0.00
BDI	−1.20	−1.36; −1.03	0.00	−0.1	−0.01; −0.01	0.00	0.91	0.73; 1.10	0.00
Constant	70.62	1.09; 87.13	0.00	0.81	0.71; 0.90	0.00	25.01	14.72; 35.30	0.00
Adjusted R^2		0.48			0.54			0.48	

^Abbreviations: ASM, antiseizure medication; B, regression coefficient; BDI, Beck Depression Inventory (Version 2); CI, confidence interval; EQVAS, EuroQol visual analogue scale; EQ5D, EuroQol-5-Dimensions Questionnaire; QOLIE10, Quality of Life in Epilepsy-10; VNS, vagus nerve stimulation.
[1] Idiopathic generalized epilepsy in comparison to focal epilepsy.
[2] VNS devices with autostimulation in comparison to VNS devices without autostimulation
[3] Response rate was defined as a reduction in seizure frequency of ≥ 50 % compared to baseline.

of SV2A modulators or slow inhibitors of sodium channels with VNS on HrQol in epilepsy. The ASMs addressed in this context were brivaracetam, eslicarbazepine, lacosamide and levetiracetam. Besides the possible synergistic effects on the seizure frequency, the amelioration of behavioral side effects of SV2A modulators by VNS is an important factor of HrQol-improvement in these combinations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Sultana B, Panzini M-A, Veilleux Carpentier A, Comtois J, Rioux B, Gore G, et al. Incidence and prevalence of drug-resistant epilepsy: a systematic review and meta-analysis. Neurology 2021;96(17):805–17.
[2] Shlobin NA, Campbell JM, Rosenow JM, Rolston JD. Ethical considerations in the surgical and neuromodulatory treatment of epilepsy. Epilepsy Behav 2022;127:108524.
[3] Skrehot HC, Englot DJ, Haneef Z. Neuro-stimulation in focal epilepsy: a systematic review and meta-analysis. Epilepsy Behav 2023;142:109182.
[4] Schulze-Bonhage A, Hirsch M, Knake S, Kaufmann E, Kegele J, Rademacher M, et al. Focal cortex stimulation with a novel implantable device and antiseizure outcomes in 2 prospective multicenter single-arm trials. JAMA Neurol 2023;80(6):588.
[5] Toffa DH, Touma L, El Meskine T, Bouthillier A, Nguyen DK. Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: a critical review. Seizure 2020;83:104–23.
[6] Polkey CE, Nashef L, Queally C, Selway R, Valentin A. Long-term outcome of vagus nerve stimulation for drug-resistant epilepsy using continuous assessment, with a note on mortality. Seizure 2022;96:74–8.
[7] Batson S, Shankar R, Conry J, Boggs J, Radtke R, Mitchell S, et al. Efficacy and safety of VNS therapy or continued medication management for treatment of adults with drug-resistant epilepsy: systematic review and meta-analysis. J Neurol 2022;269(6):2874–91.
[8] Shlobin NA, Sander JW. Current principles in the management of drug-resistant epilepsy. CNS Drugs 2022;36(6):555–68.
[9] Wang M, Perera K, Josephson CB, Lamidi M, Lawal OA, Awosoga O, et al. Association between antiseizure medications and quality of life in epilepsy: a mediation analysis. Epilepsia 2022;63(2):440–50.
[10] Winter Y, Sandner K, Glaser M, Ciolac D, Sauer V, Ziebart A, et al. Synergistic effects of vagus nerve stimulation and antiseizure medication. J Neurol 2023;270(10):4978–84.
[11] Mulhern B, Pink J, Rowen D, Borghs S, Butt T, Hughes D, et al. Comparing generic and condition-specific preference-based measures in epilepsy: EQ-5D-3L and NEWQOL-6D. Value Health 2017;20(4):687–93.
[12] Cramer JA, Perrine K, Devinsky O, Meador K. A brief questionnaire to screen for quality of life in epilepsy: the QOLIE-10. Epilepsia 1996;37(6):577–82.
[13] Kühner C, Bürger C, Keller F, Hautzinger M. Reliability and validity of the Revised Beck Depression Inventory (BDI-II). Results from German samples. Nervenarzt 2007;78:651–6.
[14] Winter Y, Daneshkhah N, Galland N, Kotulla I, Krüger A, Groppa S. Health-related quality of life in patients with poststroke epilepsy. Epilepsy Behav 2018;80:303–6.
[15] Winter Y, Uphaus T, Sandner K, Klimpe S, Stuckrad-Barre SV, Groppa S. Efficacy and safety of antiseizure medication in post-stroke epilepsy. Seizure 2022;100:109–14.
[16] Martorell-Llobregat C, González-López P, Luna E, Asensio-Asensio M, Jadraque-Rodríguez R, García-March G, et al. The role of vagus nerve stimulation in the treatment of refractory epilepsy: clinical outcomes and impact on quality of life. Neurologia (Engl Ed) 2019.
[17] Wang HJ, Tan G, Zhu LN, Chen D, Xu D, Chu SS, et al. Predictors of seizure reduction outcome after vagus nerve stimulation in drug-resistant epilepsy. Seizure 2019;66:53–60.
[18] Chen HF, Tsai YF, Hsi MS, Chen JC. Factors affecting quality of life in adults with epilepsy in Taiwan: a cross-sectional, correlational study. Epilepsy Behav 2016;58:26–32.
[19] Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–105.
[20] Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia 2007;48(12):2336–44.
[21] Kanner AM. Depression in epilepsy: a neurobiologic perspective. Epilepsy Curr 2005;5(1):21–7.
[22] Wang H, Chen X, Lin Z, Shao Z, Sun B, Shen H, et al. Long-term effect of vagus nerve stimulation on interictal epileptiform discharges in refractory epilepsy. J Neurol Sci 2009;284(1-2):96–102.
[23] Niespodziany I, Klitgaard H, Margineanu DG. Desynchronizing effect of levetiracetam on epileptiform responses in rat hippocampal slices. Neuroreport 2003;14(9):1273–6.
[24] Georg Margineanu D, Klitgaard H. Inhibition of neuronal hypersynchrony in vitro differentiates levetiracetam from classical antiepileptic drugs. Pharmacol Res 2000;42(4):281–5.
[25] Klitgaard H, Matagne A, Nicolas JM, Gillard M, Lamberty Y, De Ryck M, et al. Brivaracetam: Rationale for discovery and preclinical profile of a selective SV2A ligand for epilepsy treatment. Epilepsia 2016;57:538–48.