



QUALITY OF LIFE IN PATIENTS WITH EPILEPSY – SINGLE CENTRE EXPERIENCE

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SUMMARY – A prospective study was carried out at the Zagreb University Hospital Centre to evaluate the relationship between epilepsy, antiepileptic drugs (AEDs) and quality of life (QoL) in patients with epilepsy (PE), and its association with depressive symptoms and sexual dysfunction (SD). QoL was assessed by use of the Quality of Life in Epilepsy-31 Inventory (QOLIE-31), SD by the Arizona Sexual Experiences Scale (ASEX), and depressive symptoms by the Hamilton Rating Scale for Depression (HAM-D17). The study included 108 PE (women 63% and men 37% men), mean age 39.54±15.91 years. Focal type epilepsy was diagnosed in 14.8%, generalized type in 35.2%, and both types were present in 40.7% of study patients. Drug-resistant epilepsy (DRE) was present in 44/108 and vagus nerve stimulation (VNS) was implanted in 27/44 patients. The mean response on QOLIE-31 was 62.88±17.21 with no significant differences according to gender, type of epilepsy, and age. A statistically significantly lower QoL was found in the 'Overall QoL' domain (35-55 *vs.* <35 age group). Patients taking both types of AEDs had a significantly lower QoL compared to those on newer types of AEDs. Higher QoL was associated with less pronounced depressive symptoms ($p=0.000$). Significant correlations were found between lower QoL and SD ($p=0.001$). In 27 patients with DRE having undergone VNS, a favorable effect of VNS implantation on the QoL and mood was observed as compared with 18 patients without VNS ($p=0.041$).

Key words: *Epilepsy; Quality of life; Antiepileptic drugs; QOLIE-31; Drug-resistant epilepsy; Vagus nerve stimulation*

Introduction

The World Health Organization (WHO) defines quality of life (QoL) as “an individual’s perception of their position in life in the context of the culture and

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value systems in which they live and concerning their goals, expectations, standards, and concerns"¹. Patients with epilepsy as a chronic disease are at risk of impaired health-related quality of life (HRQoL), which is not solely confined to the fear of recurrent seizures and physical injury associated with seizures but also to the risks of treatment-related side effects, lifestyle restrictions, physical difficulties, and perceived stigmatization that frequently results in social exclusion and isolation, as well as difficulties in accessing educational services and obtaining employment due to the presence of cognitive or psychiatric problems²⁻⁴.

Psychiatric comorbidities and disorders such as depression, anxiety, psychosis, inattention, obsession, personality traits, aggression, and suicide are frequent in patients with epilepsy and have a significant impact on medical management and QoL⁵. They are related not only to psychosocial factors but also to structural (epilepsy process and epileptogenesis) mechanisms, as well as an adverse effect of antiepileptic drugs (AEDs). Epilepsy and depression seem to have a bidirectional association, in probably shared pathophysiological mechanism caused by impairment of cellular metabolism associated with the process of epileptogenesis, neuronal plasticity and changes in hypothalamic-pituitary axis (HPA), neurotransmitters and pathways due to epilepsy. Furthermore, increasing GABA-mediated inhibitory activity, glutamate blockage activity, alteration of serotonergic, adrenergic and noradrenergic neurotransmitters and pathways might contribute to behavioral changes associated with AEDs^{3,5,6}. The risk of depression and other psychiatric disorders appears to be particularly high in epilepsy patients with intellectual disability. Furthermore, anxiety about seizures, added to the actual occurrence of seizures, has also been shown to be one of the most important factors affecting QoL in patients with epilepsy^{3,6}.

The incidence of sexual dysfunction (SD) in male patients with epilepsy is 5 times higher compared to healthy population, and the incidence of sexual hyperactivity is about 2.9%⁷. Sexual disturbances are not only influenced by AEDs but also by epilepsy itself, especially in temporal lobe epilepsy, where abnormal brain epileptiform discharges may directly interfere with the function of the hypothalamic-pituitary-gonadal axis, which may cause abnormalities in the secretion of sex hormones and lead to reproductive endocrine disorders^{7,8}. Studies have shown that AEDs, es-

pecially older ones such as carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB) that are enzyme inducer classes, and valproate (VPA) as liver enzyme inhibitor can cause endocrine disorders in male patients with epilepsy and lead to a decrease in fertility⁹. Newer AEDs, oxcarbazepine (OXC), levetiracetam (LEV), or lamotrigine (LTG) might affect sexual function less than older AEDs, and some studies have shown that these AEDs have no significant effect on sexual function and sex hormones⁸.

Current treatment options for patients with drug-resistant epilepsy (DRE) include pharmacotherapy with AEDs, surgical removal of the seizure focus, and alternative approaches such as neurostimulation, ketogenic diet, and lifestyle changes¹⁰. Vagus nerve stimulation (VNS) is a viable, minimally invasive neurosurgical treatment option for DRE. As the published studies on VNS in epilepsy have reported improvement in QoL after VNS implantation¹¹, we included patients with implanted VNS in our study.

As there are different variables influencing QoL, in addition to different psychiatric comorbidities and SD that further decrease QoL, QoL has recently been increasingly measured in epilepsy patients in clinical and research practice using a variety of surveys, scales, and questionnaires that study particular cohorts of patients with epilepsy, impact of seizure treatments, epilepsy surgery, cultural differences and patient education, as well as other parameters influencing their QoL¹².

Patients and Methods

Participants

A prospective cross-sectional study was conducted at the Department of Neurology, Referral Centre of the Ministry of Health of the Republic of Croatia for Epilepsy, Zagreb University Hospital Centre, Zagreb, Croatia (a tertiary teaching hospital) to assess the impact of AEDs and VNS treatment on the QoL of our patients with epilepsy during the period of 18 months. The study was approved by the Ethics Committee of the Zagreb University Hospital Centre and all participants gave their informed consent to participate in the study.

The study included 108 patients with epilepsy. Demographic data were recorded, as well as data from patient history, e.g., gender, age, clinical phenotype of

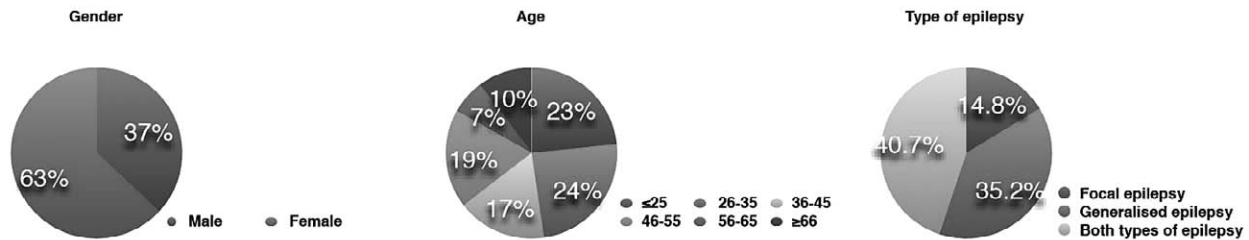


Fig. 1. Graphic presentation of gender, age, and type of epilepsy in study patients.

seizures (focal, generalized, or combined focal and generalized epilepsy), and co-administered AEDs (new: lacosamide – LCS, LTG, LEV, OXC; pregabalin – PGB; topiramate – TPM; zonisamide – ZNS; and old: acetazolamide – ACT, CBZ; clobazam – CLB; clonazepam – CLN; ethosuximide – ESC; methylphenobarbital – MPB; sulthiame – SUL, VPA). The group of patients with DRE (n=44) included those with implanted VNS (n=27).

Questionnaires

Three questionnaires evaluating QoL, depressive symptoms and SD were administered to consecutive patients on their follow-up visits to the Referral Centre of the Ministry of Health of the Republic of Croatia for Epilepsy, Zagreb, Croatia.

Quality of life was assessed using the Quality of Life in Epilepsy Inventory-31 items (QOLIE-31) as the most widely used questionnaire previously validated for Croatian language and population. This scale contains seven multi-item scales that enquire the following domains: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. The weighted average of these domains together makes an overall score and the QOLIE-31 also includes a single item that assesses overall health^{13,14}.

Depressive symptoms were evaluated using the Hamilton Rating Scale for Depression (HAM-D17), the most widely used clinician-administered depression assessment scale¹⁵, while SD was evaluated using the Arizona Sexual Experience Scale (ASEX), a questionnaire commonly used in clinical trials to assess sexual functioning¹⁶. The latter two were not in the focus of this study and their purpose here was to give an insight into the relationship of QoL with depressive symptoms and SD.

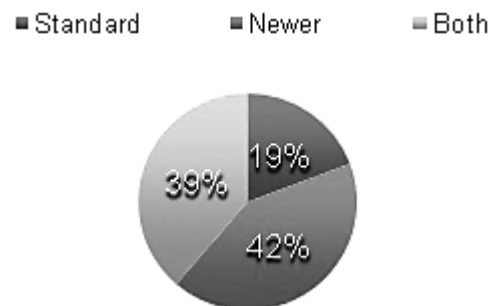


Fig. 2. Antiepileptic drug therapy in study patients.

Statistical analysis

All statistical data analyses were performed using SPSS version 20.0¹⁷. The following statistical tests were performed: t-test for means correlations, one-way ANOVA, post hoc Scheffe test for multiple comparisons, Bonferroni correction test for multiple univariate analyses, Tukey test and Pearson correlation coefficient for scale data associations. The Mann-Whitney test was performed for nonparametric two-sample analysis.

Results

The study included 108 patients with epilepsy, mean age 39.54±15.91 (range 18–80) years. There were 68 (63%) women and 30 (37%) men, mean age 38.07±16.14 (range 18–77) and 42.102±15.37 (18–80) years, respectively. Sixteen (14.8%) patients had focal, 38 (35.2%) generalized and 44 (40.7%) both types of epilepsy. The majority of patients (24%) were in the 26–35 age group (Fig. 1). The majority of patients (n=71, 65.74%) were treated with two or more AEDs, and 25% (n=27) were treated with one AED. The majority (42%) of patients were treated with new AEDs, 39% with both types of AEDs, and 19% with old AEDs (Fig. 2).

Table 1. Mean results on QOLIE-31 according to gender (group statistics)

	Gender	N	Mean	SD	SE
QOLIE-31	Men	35	62.1899	18.51495	3.12960
	Women	57	63.3159	16.51644	2.18766

QOLIE-31 = Quality of Life in Epilepsy-31 Inventory; SD = standard deviation; SE = standard error of mean

Table 2. QOLIE-31 mean response according to gender (independent samples test)

		QOLIE-31_total	
		Equal variances assumed	Equal variances not assumed
Levene's test for equality of variances	F	0.49300	
	Sig.	0.48400	
t-test for equality of means	t	-0.30300	-0.29500
	df	90	65.80500
	Sig. (2-tailed)	0.76300	0.76900
	Mean difference	-1.12597	-1.12597
	Std. error difference	3.71478	3.81841
	95% confidence interval of difference	Lower	-8.50603
	Upper	6.25409	6.49814

QOLIE-31 = Quality of Life in Epilepsy-31 Inventory

The mean response on the QOLIE-31 was 62.88 ± 17.21 (range 15.48-89.06); the mean overall response was 63.31 ± 16.51 in women and 62.18 ± 18.51 in men (Table 1). There were no significant gender differences in the QOLIE-31 (Table 2). Except for the 'Overall QoL' domain, found to be statistically significantly lower in the '35-55 age group in comparison to the <35 age group, no other statistically significant differences were recorded according to age and QOLIE-31 responses. We found no statistically significant differences according to the type of epilepsy and QOLIE-31 results either.

There was a statistically significant difference in QOLIE-31 responses between patients treated with new AEDs and those treated with both types of AEDs ($p=0.002$). The latter had a significantly lower QoL. Also, QoL was found to be significantly lower in both men and women treated with both types of AEDs in comparison to those treated with new AEDs. Women treated with old AEDs had better QoL than those treated with new AEDs and with both types of AEDs. Men treated with new AEDs were found to have better QoL when compared to those treated with old AEDs and with both types of AEDs (Fig. 3).

When analyzing different domains on QOLIE-31 and interaction with AEDs, statistically significant differences ($p<0.05$) were found on the following domains: 'Seizure worry' was more pronounced in those treated with new AEDs as compared to those treated with both types of AEDs; 'Overall quality of life' revealed better QoL in those treated with new AEDs as compared to those treated with both types of AEDs; 'Emotional wellbeing' yielded lower emotional wellbeing scores in those treated with old AEDs as compared to those treated with new AEDs; 'Cognitive functioning' and 'Social functioning' showed higher, i.e. better scores in patients treated with old and new AEDs as compared to patients taking both types of AEDs. No significant differences were found in the 'Energy/fatigue' and 'Medication effects' domains according to the type of AEDs.

We found a strong negative correlation between higher QoL and HAM-D17 ($p=0.000$). Significant correlations were found between lower QoL and SD ($p=0.001$). Higher QoL was found to be associated with less pronounced symptoms of SD ($r=-0.34$) and depression ($r=-0.71$), whereas more pronounced SD symptoms were associated with more pronounced depressive symptoms ($r=0.35$) (Table 3).

Additionally, our study group included 44 patients with DRE, including 27 patients treated with VNS and six patients underwent epilepsy surgery due to mesial temporal sclerosis (selective amygdalohippocampectomy, n=4), focal cortical dysplasia (n=1) and cavernoma (n=1). These patients were divided into two groups: 27 patients with implanted VNS as case group (14 M, 13 F; mean age 34.7±28.3) and 18 control patients with DRE without implanted VNS (10 M, 8 F; mean age 45.2±30.8). The mean response on the QO-

LIE-31 was 69.47±16.23 in patients treated with VNS *versus* 52.9±20.62 in the control group. Mann-Whitney test yielded a significant difference in the QOLIE-31 score between the case group and control group (p=0.041). In the case group, younger patients had a lower QOLIE-31 score, but the difference was not statistically significant.

Discussion

In our study, the mean response on QOLIE-31 was 62.88±17.21, which is slightly higher than the global mean QOLIE-31 score of 59.8¹⁸. We found no statistically significant QoL difference according to the type of epilepsy seizures, and in the literature, there is a controversy regarding the type of seizures that mostly affects QoL. Some studies indicate that people with generalized epilepsy have lower QoL, whereas others report on focal epilepsy association with lower QoL, but most studies could not find strong correlation between seizure types and QoL but emphasize the impact of seizure frequency and duration of epilepsy on QoL¹⁹⁻²¹.

Our results showed gender differences, meaning that our female patients reported better QoL than men. This is different from literature data, where some studies support the hypothesis of no gender differences in QoL, and others do not; however, in those that do it women's QoL is always rated lower than men's QoL. Some of the factors resulting in lower QoL are partially explained with lower medical care and poorer social support for women in low-income

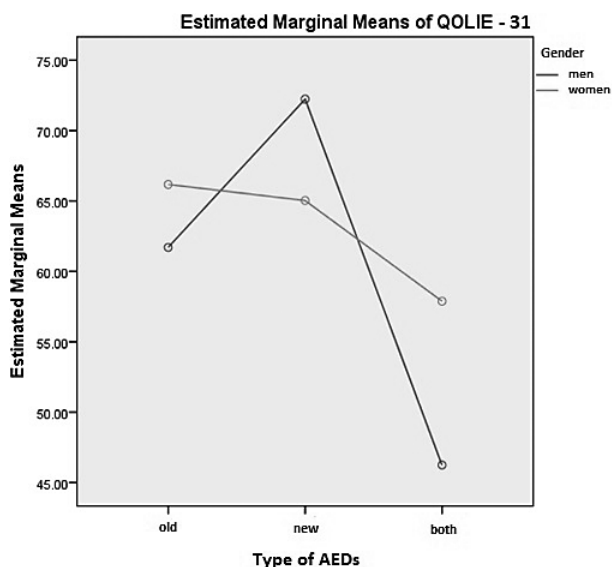


Fig. 3. Mean QOLIE-31 differences between men and women according to AED treatment.

QOLIE-31 = Quality of Life in Epilepsy-31 Inventory; AEDs = antiepileptic drugs

Table 3. Correlations among the QOLIE-31, HAM - D17 and ASEX questionnaires

		QOLIE-31_total	ASEX_total	HAM- D17_total
QOLIE-31_total	Pearson correlation	1	-0.339**	-0.705**
	Sig. (2-tailed)		0.001	0.000
	n	92	85	72
ASEX_total	Pearson correlation	-0.339**	1	0.347**
	Sig. (2-tailed)	0.001		0.003
	n	85	94	72
HAM- D17_total	Pearson correlation	-0.705**	0.347**	1
	Sig. (2-tailed)	0.000	0.003	
	n	72	72	79

QOLIE-31 = Quality of Life in Epilepsy-31 Inventory; HAM- D17 = Hamilton Rating Scale for Depression; ASEX = Arizona Sexual Experience Scale; **correlation significant at the 0.01 level (2-tailed)

countries, and with different psychosocial factors in developed countries²²⁻²⁴.

When comparing different age groups, we did not find statistically significant differences in QOLIE-31 on the overall score, but it was found to be statistically significantly lower in the 'overall QoL' subscale in the 35-55 age group as compared to the <35 age group. When looking into the literature on patients with epilepsy, their age and gender did not show any significant impact on QoL²³. In our study, we did not compare patients with epilepsy to healthy controls, but in previous studies, it has been reported that patients with epilepsy have lower QoL compared to healthy controls²⁵⁻²⁷.

Patients taking modern AEDs have better QoL compared to those taking both old and modern AEDs ($p=0.002$), which applies to both men and women. It is generally assumed that modern AEDs have the same efficacy as older ones and better tolerability, but they also have side effects, especially cognitive and psychiatric. As this was a tertiary level center investigation, many of the patients enrolled in the study had DRE with seizures difficult to treat and leading to AED polytherapy. Furthermore, although monotherapy is preferred, there is evidence for the efficacy of combination AEDs with different or multiple mechanisms of action for better seizure control. According to literature data, polytherapy is associated with a higher level of AEDs, associated side effects, and lower QoL¹⁰. Other studies such as SANAD have demonstrated that newly diagnosed patients with epilepsy are cognitively compromised before starting AED treatment and that the domains most affected were memory and psychomotor speed, which leads to a conclusion that seizures may themselves result in cognitive impairment²⁸. On the other hand, cognitive impairment increases the likelihood of physical injury in patients with epilepsy, thus all resulting in lower QoL^{3,4}. In our study patients taking only modern or old AEDs reported better cognitive functioning than patients taking both old and modern AEDs.

Our study patients taking modern AEDs reported better emotional well-being compared to patients taking old AEDs. Thus, according to literature data, psychiatric and behavioral side effects occur more frequently in patients taking new AEDs (LEV, ZNS), whereas lower rates were seen in patients taking old AEDs, i.e. CBZ, CLB, gabapentin (GBP), lamotrigine

(LTG), oxcarbazepine (OXC), PHT and VPA. Higher rates of side effects with new AEDs caused higher rates of intolerability and led to AED discontinuation²⁹. The relationship between psychiatric disorders and epilepsy has relevant therapeutic implications, which should be directed towards a comprehensive biopsychosocial approach focused on the persons as a whole rather than simply on the disease process⁶. In our study, we found a strong negative correlation between higher QoL and HAM-D17 ($p=0.000$), meaning that patients with pronounced depressive symptoms had lower QoL.

Patients taking modern AEDs are more worried about seizures than patients taking both modern and old AEDs, both women and men. This is probably to some extent due to the belief of our patients that old AEDs are more potent in reducing seizure frequency, and is consistent with the fact that seizure frequency and seizure types are two of the most important factors influencing QoL in patients with epilepsy. Fear of and worrying about having a seizure are common in patients with epilepsy, resulting in lowest scores on the 'Seizure worry' subscale compared to other subscales, both in men and women^{12,19,30}.

Social functioning was better in patients taking old or modern AEDs compared to patients taking both old and modern AEDs. Social functioning is to some extent influenced by the stigma associated with epilepsy as a chronic illness, resulting in discrimination in everyday activities, such as attending school, driving, working, and obtaining insurance^{12,31,32}. Deficiencies in social well-being may arise due to psychological factors resulting in impairment of the development of skills needed for social interaction such as parental overprotectiveness in childhood, stigmatization, reduced life experience opportunities, and fear of seizures. Furthermore, psychiatric symptoms such as depression and anxiety, or neurocognitive impairments in attention, memory, language, and processing speed, which are all common in patients with epilepsy, can contribute to social difficulties³². Also, a higher education level of patients with epilepsy seems to be associated with better QoL, thus promoting the idea of continuing education and better social functioning in patients with epilepsy³³. Other data suggest a strong correlation between seizure frequency and polypharmacy, and their association with poorer QoL^{27,34-36}.

Modern treatment options for patients with DRE include pharmacotherapy with AEDs, surgical removal of the seizure focus, and alternative approaches such as neurostimulation, ketogenic diet, and lifestyle changes¹⁰. VNS was approved in 1997 as adjunctive therapy for patients with DRE. Since then, VNS therapy has been provided to around 100,000 patients worldwide, and its beneficial effects in reducing seizure frequency have been reported in multiple long-term open-label studies. Furthermore, studies showed other potential benefits that reach beyond seizure reduction, decrease in the severity and duration of ictal or postictal phases but also benefits from improvement in mood, vigilance, communication and cognition, and the possibility of reducing AEDs and associated adverse effects. Thus, this leads to a conclusion that VNS-related improvement in HRQoL might reflect the sum of all these benefits or be mediated by these multiple factors¹¹. This was also shown in our study, where patients with DRE reported higher QOLIE-31 scores as compared to DRE patients treated solely with AEDs.

Conclusion

Epilepsy is highly comorbid with other cognitive, physical and psychiatric disorders, which often additionally limit patient functional abilities in everyday functioning and it is therefore important to focus not only on the efficacy of AEDs or neurosurgery but to look at the patient in a more holistic manner, including comorbidities, side effects, and their overall QoL. The results of this study evaluating QoL in epilepsy patients demonstrated that patients taking both types of AEDs had significantly lower QoL in comparison to those on new AEDs. Higher QoL is associated with less pronounced depressive symptoms and SD. Also, our results in DRE patients showed that patients having undergone VNS reported better QoL compared to patients without VNS, and according to literature data, this effect may be the result not only of seizure reduction but multifactorial (i.e. mood improvement, vigilance, cognition).

The major limitation of this study was the lack of comparison with healthy population of Croatia. Furthermore, our results mostly reflect the QoL of patients with pharmacoresistant epilepsy, as this is a Referral Centre for Epilepsy for our country, where most

difficult cases have been treated. Also, this was a single-center study with a small sample size. In the future, studies that will enroll more patients in comparison to healthy controls, performed with appropriate multivariate statistical methods that prospectively investigate the factors influencing QoL in patients with epilepsy are needed.

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Sažetak

KVALITETA ŽIVOTA BOLESNIKA S EPILEPSIJOM – NAŠA ISKUSTVA

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Provedeno je prospektivno istraživanje u KBC-u Zagreb s ciljem procjene povezanosti epilepsije, antiepileptičkih lijekova (*antiepileptic drug*, AED) i kvalitete života (*quality of life*, QoL) u bolesnika s epilepsijom, kao i učestalosti depresije i seksualne disfunkcije (SD). QOLIE-31 (*Quality of Life in Epilepsy-31 Inventory*) je primijenjen za procjenu QoL-a, ASEX (*Arizona Sexual Experiences Scale*) za SD i HAM-D17 (*Hamilton Rating Scale*) za depresiju. Uključeno je 108 bolesnika s epilepsijom (63% žena, 37% muškaraca; srednja dob 39,54±15,91 godina). Žarišnu epilepsiju imalo je 14,8% i generaliziranu 35,2% bolesnika, dok je obje vrste epilepsije imalo 40,7% bolesnika. Farmakorezistentnu epilepsiju (*drug-resistant epilepsy*, DRE) imalo je 44/108 bolesnika, a kod njih 27/44 ugrađen je stimulator vagusnog živca (*vagus nerve stimulation*, VNS). Srednji odgovor na QOLIE-31 bio je 62,88±7,21 bez značajnih razlika u odnosu na spol, vrstu epilepsije i dob. Statistički značajno niži QoL nađen je u domeni 'Sveukupni QoL' (dobna skupina 35-55 godina u odnosu na dobnu skupinu <35). Bolesnici koji su uzimali obje vrste AED imali su značajno niži QoL u usporedbi s onima na novijim AED. Viši QoL bio je povezan s manje izraženim simptomima depresije (p=0,000). Pronađene su značajne korelacije između nižeg QoL-a i SD (p=0,001). U bolesnika s DRE utvrđen je pozitivan utjecaj ugradnje VNS-a na QoL i raspoloženje (27 bolesnika s VNS-om u usporedbi s 18 bolesnika bez VNS-a, p=0,041).

Ključne riječi: *Epilepsija; Kvaliteta života; Antiepileptički lijekovi; QOLIE-31; Farmakorezistentna epilepsija; Stimulator vagusnog živca*