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# Depression and quality of life in patients with epilepsy in Northwest Greece

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ABSTRACT

*Purpose:* The purpose of the present study was to compare depression and QoL between patients with epilepsy and healthy controls, evaluating potentially related factors to depression and QoL in patients with epilepsy in Northwest Greece.

*Methods:* A case study was conducted in adult patients with epilepsy followed up at the University Hospital of Ioannina and in healthy controls. The Patient Health Questionnaire (PHQ-9) for depression's severity evaluation, the WHOQOL-BREF questionnaire for the QoL estimation and the Adverse Event Profile (AEP) questionnaire for the Antiepileptic Drugs (AEDs) adverse effects assessment were used.

*Results:* Seventy patients with epilepsy and 70 controls were recruited. The PHQ-9 score was higher in patients compared to controls and slightly higher than reported in patients with epilepsy. PHQ-9 was significantly associated with the AEP score. Our patients had a poorer QoL compared to controls. The level of education, the AEP and the PHQ-9 scores were associated to QoL, the last two being the most powerful predictors of QoL.

*Conclusion:* Patients with epilepsy in Northwest Greece had higher rates of depression than reported in patients with epilepsy and poorer QoL compared to controls. The adverse effects of AEDs were related to depression in our study, while the adverse effects of AEDs and depression were more powerful predictors of QoL compared to demographics and other characteristics of epilepsy.

## 1. Introduction

Epilepsy is a frequent neurological disorder with a prevalence of 6.38 per 1000 persons [1] and approximately 5 million people have been diagnosed with epilepsy worldwide, according to the World Health Organization (WHO). Patients with epilepsy have a three-fold risk for psychiatric comorbidities compared to the general population [2]. Almost 20–22% of patients with epilepsy suffer from depression [2–7], while its prevalence may reach 60% in patients with temporal lobe epilepsy [8,9].

The early recognition and treatment of depression in patients with epilepsy is of high importance since patients with epilepsy suffering from depression tend to use health care services more frequently [10] and have a poorer quality of life (QoL) compared to patients without depression [11–14]. Furthermore, suicide ideation, which is higher in patients with epilepsy compared to the general population, may be connected to depression [15].

Depression has been established as one of the stronger predictors of poor QOL in patients with epilepsy [11,13,14]. Regarding the characteristics of epilepsy, the frequency of seizures and the adverse effects of antiepileptic drugs (AEDs) are also important parameters that may determine QoL [16,17].

The aim of the present study is to descriptively compare the presence of depression in patients with epilepsy and healthy controls in an urban area of Northwest Greece. Subsequently, a comparison of QoL in patients with epilepsy and in healthy controls is presented. In patients with epilepsy, we elucidate causing factors that have a potential impact on depression and QoL and the association of depression with QoL.

## 2. Materials and methods

### 2.1. Participants

All consequent adult patients with epilepsy followed up at the Adult Epilepsy Outpatient Clinic of the University Hospital of Ioannina (Ioannina, Northwest Greece, Greece) were enrolled in the study from

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To be eligible, patients must have been diagnosed with epilepsy for more than a year and be under antiepileptic drugs (AED) treatment. The control group consisted of race, gender and age matched to patients with epilepsy group individuals and were healthy non-relative visitors of hospitalized patients.

Exclusion criteria included mental retardation, the diagnosis of psychogenic non-epileptic attacks, alcohol or any addiction, history or presence of major psychotic disorder and seizures occurring in the past two days prior to their enrollment. To ensure lack of mental retardation, participants were assessed with the Montreal Cognitive Assessment (MOCA) [18]. To ensure that participants do not suffer from a major psychotic disorder or alcohol/drug addictions, the Mini International Neuropsychiatric Interview (MINI) Greek Version 5.0.0, based on Diagnostic and Statistical Manual of Mental Disorders 4$^{th}$ edition (DSM-IV), was used. MINI has been previously used in epilepsy [19,20] and is validated in the Greek population [21,22].

Demographic data of each participant was recorded, such as age, gender, level of education (6 years of education, 12 years of education and university studies) and marital status (married and non-married, in which non-married status includes single, widowed and divorced). The presence of depression and whether or not the participants were under antidepressant drugs treatment was also recorded.

Data from the medical history of patients with epilepsy was also recorded, such as the age of epilepsy onset, duration of epilepsy in years, seizure frequency and the type of epilepsy, (generalized epilepsy, focal epilepsy, and of unknown origin) [23]. Brain MRI findings were recorded and patients were divided into those having findings in the MRI and those who did not. The administered Antiepileptic drugs (AEDs), the number of administered AEDs at the time of recruitment, as well as the total number of AEDs prescribed until now were recorded. Patients were further categorized according to whether their therapeutic schema included mood stabilizers (such as valproate, lamotrigine, carbamazepine and oxcarbazepine/eslicarbazepine) or not.

To evaluate adverse effects of AEDs, patients with epilepsy completed an Adverse Event Profile (AEP) questionnaire for AEDs. The AEP consists of 19 questions referring to the most common adverse effects of AEDs, on a scale of 1–4, according to their frequency. The minimum score is 19 points and the maximum is 76. The higher the AEP score, the more adverse effects the patient experiences. AEP is a reliable questionnaire commonly used in epilepsy research [11,24,25].

The study was approved by the Medical Ethical Committee of the University Hospital of Ioannina and all participants gave their informed consent to participate.

### 2.2. Questionnaires

The presence and the severity of depression in patients and controls were evaluated using the Patient Health Questionnaire 9 (PHQ-9). The PHQ-9, is comprised of 9 items, is self-completed, easily scored and is an acceptable method for depression and depression severity assessment. It is also valid for the screening of depression in adults with epilepsy [26]. Its specific items are designed to establish the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria-based diagnosis of Major Depressive Disorder (MDD). The PHQ-9 rates the frequency of symptoms of anhedonia, depressed mood, trouble sleeping, fatigue, changes in appetite, feelings of guilt or worthlessness, trouble concentrating, feeling weak or restless (psychomotor excitation/poverty), and experiencing suicidal thoughts over the past 2 weeks on a 0–3 scale. The final score is calculated from the sum of each answer, with a minimum score of 0 points and a maximum of 27 points. The diagnosis of MDD is suggested when the PHQ-9 $\geq$ 10 [24,25].

The QoL in patients and in controls was evaluated with the BREF-(World Health Organization) WHO Quality of Life questionnaire (WHOQOL-BREF). WHOQOL-BREF consists of 24 questions considering four domains: physical health, psychological, social relationships and environmental. The physical health domain assesses a patient's daily activities, dependence on substances, energy and fatigue, mobility, pain and discomfort, sleep and rest and work capacity. The psychological domain assesses appearance, negative/positive feelings, self-esteem, spirituality / religion / beliefs and thinking, learning, memory and concentration. The social relationships domain assesses personal relationships, social support and sexual activity. The environmental domain assesses financial status, freedom, safety and security, health and social care, home environment, opportunities for new information and skills, recreation / leisure activities, environment and transport [27]. The scores of these four domains were transformed according to the WHOQOL-BREF manual, to a 0–100 scale [27] with higher domain scores denoting higher QoL. WHOQOL-BREF is a reliable instrument, exploring all the aforementioned dimensions of QoL and is suitable for both patients and participants in healthy controls. WHOQOL-BREF is an assessment tool that has been previously used in patients with epilepsy [28].

The Greek version was used for both questionnaires [16,29].

The PHQ-9 total score, the MDD (PHQ-9 $\geq$ 10) frequency and the four domains of QoL were analyzed comparatively for patients with epilepsy and in controls.

For the patients with epilepsy, the effects of demographics and epilepsy characteristics on PHQ-9, MDD frequency and QoL were evaluated.

The association of PHQ-9 and MDD frequency with the domains of QoL were also assessed.

### 2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0. NY, USA. For univariate analyses, *t*-test for means' correlations, Chi-square correlation for categorical data, Pearson correlation for scale data associations and Spearman's correlation for categorical data were used. Bonferroni correction test was applied for multiple univariate analyses.

Multivariate analysis was performed for PHQ-9 and QoL domains. For the most parsimonious models to be obtained, only independent variables significantly associated ($p < .05$) were included. Multivariate Forward Linear analysis was run for PHQ-9. For the QoL domains, four Hierarchical Regression analyses were run to estimate the proportion of variances. Three steps were conducted based on previous research [30–32]. In the first step, demographic factors were included. In the second step the epilepsy characteristics were added and in the final step, the depression represented from the PHQ-9 score was entered. Fig. 1 shows a graphical representation of the hierarchical models tested in the present analysis.

## 3. Results

Seventy patients with epilepsy (M/F:31/39), with a mean age of 38.3 ± 13.92 and 70 healthy controls (M/F:34/36), with a mean age of 39.5 ± 9.9 were recruited in the study. Participants' characteristics are shown in Table 1.

### 3.1. Patients vs controls

Patients with epilepsy had a significantly higher PHQ-9 score and MDD frequency compared to healthy controls (Table 2).

Patients with epilepsy had significantly lower physical health, psychological and social relationships related QoL compared to controls. Patients with epilepsy and in controls had no significant difference in the environmental domain of QoL (Table 2).

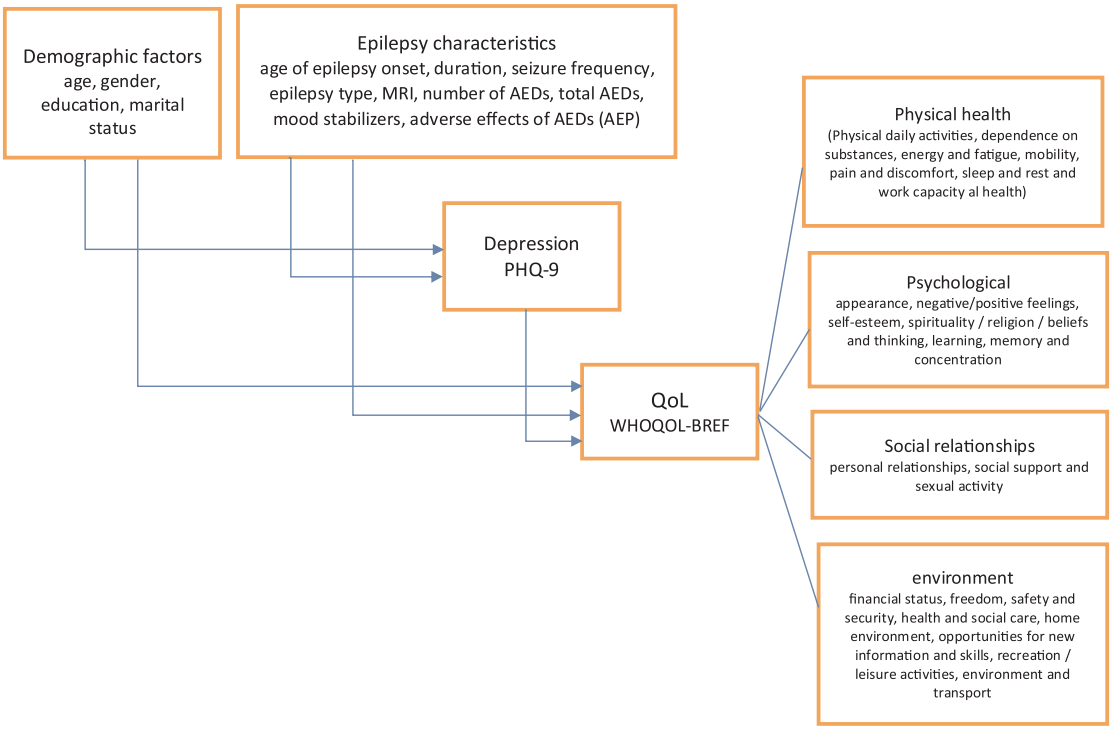


**Fig. 1.** Diagram of the hierarchical models tested for investigating the relative contribution of demographics, epilepsy and depression in the four QoL domains.

### 3.2. Patients with epilepsy

Twelve out of 20 (60%) patients with epilepsy and MDD had already been diagnosed with depression and were under the treatment of antidepressant drugs. Consequently, in 8 of the 20 (40%) patients with epilepsy and MDD, depression was undiagnosed.

All possible correlations of demographic and epilepsy characteristics with depression (PHQ-9 score) and QoL (physical health, psychological, social, environment) were performed, as well as correlations of depression with QoL domains, as shown in Table 3.

A Bonferroni correction test for multiple univariate analyses was performed and statistically significant correlations were considered when $p < 0.004$ level was reached.

The regression model showed that the seizure frequency and the AEP score accounted for 37.1% of the variance in PHQ-9 ($R^2 = 0.371$, Adjusted $R^2 = .362$, $F(1,68) = 40.1$, $p < .001$). The AEP score remained a significant coefficient ($B = 0.33$, standard error $= 0.05$, $\beta = 0.61$, $p < .001$).

The Hierarchical Regression Analyses for QoL are presented in Table 4. Regarding physical health-related QoL, the demographic factors accounted for 13%, epilepsy characteristics 32% and depression 4% of the variance accordingly. When concurrently put in the model, they accounted 46% of the variance. For psychological-related QoL, epilepsy characteristics accounted 31% and depression 17% of the variance accordingly. When concurrently put in the model, they accounted 46% of the variance. For social relationships- related QoL, epilepsy characteristics accounted 21% and depression 6% of the variance accordingly. When concurrently put together in the model, they accounted 22% of the variance. For environment-related QoL, demographic factors accounted 13%, epilepsy 15% and depression 8% of the variance accordingly. When concurrently put all together in the model, they accounted 30% of the variance.

### 3.3. Patients with epilepsy and MDD vs patients without MDD

Patients with epilepsy and MDD had no differences in demographic factors and epilepsy characteristics but had a significantly higher AEP score ($46 \pm 9.6$) compared to patients without ($35 \pm 10.9$), ($p < .001$). The physical health related QoL of patients with MDD was significantly lower ($47.86 \pm 20.48$) compared to patients without ($67.21 \pm 15.97$), ($p < .001$) and there was lower psychological QoL ($45.21 \pm 18.84$) compared to patients without ($69.5 \pm 15$), ($p < .001$). Patients with epilepsy and MDD had a lower social and environmental QoL compared to patients without but after Bonferroni correction were not significant.

## 4. Discussion

The present study is a case study conducted in patients with epilepsy and healthy controls, in Northwest Greece with the objective to compare the presence and the severity of depression and QoL between patients with epilepsy and in healthy controls and to detect potential factors that affect depression and QoL in patients with epilepsy in the region.

### 4.1. Depression

Our results showed that depression was considerably more common in patients with epilepsy compared to healthy controls, with 1 in 4 patients with epilepsy suffering from MDD. Forty percent of these patients were undiagnosed. The adverse effects of AEDs were significantly associated to depression in our study.

The prevalence of MDD in patients with epilepsy has been estimated to be 20–22%, when DSM-IV criteria is used [6,33,34]. MDD prevalence in the general population is estimated around 2.4–3.8% [35].

In the literature, the age of patients is not found to be associated to depression [36,37]. Female gender could be considered a risk factor for depression in epilepsy [38], although there are also studies that have not detected a significant association between gender and depression [36,37]. However, the higher the level of education was, the lower the incidence of depression has been recorded [39]. Single patients with epilepsy may be at a greater risk for depression compared to those who are married [40], although a link between marital status and depression in patients with epilepsy had not been always confirmed

**Table 1**
Characteristics of sparticipants and clinical characteristics of patients with epilepsy.

| | | PWE | controls | sig.(2-tailed) |
|---|---|---|---|---|
| total n = | | 70 | 70 | 1 |
| age | | 38.3 ± 13.92 | 39.5 ± 9.9 | p > .05 |
| females | | 39(55.7%) | 36(51.4%) | p > .05 |
| males | | 31(44.3%) | 34(48.6%) | p > .05 |
| education level | **≤ 6 years** | 4 (5.7%) | 1 (1.4%) | |
| | **7-12 years** | 40 (57.1%) | 22 (31.4%) | p < .01 |
| | **university** | 26 (37.1%) | 47 (67.1%) | |
| married | | 37 (52.9%) | 43 (61.4%) | p > .05 |
| depression diagnosis/antidepressants | | 12(17.1%) | 2(2.4%) | p < .01 |
| age at 1st seizure | | 20.8 ± 12.6 | | |
| epilepsy duration(years) | | 16.9 ± 13.4 | | |
| seizure frequency | **no seizure for a year** | 8(11.4%) | | |
| | **≥1 seizure per year** | 36(51.4%) | | |
| | **1-3 seizures per month** | 12(17.1%) | | |
| | **1 seizure per week** | 12(17.1%) | | |
| | **> 1 seizure per week** | 2(2.9%) | | |
| epilepsy type | **generalized** | 32(45.7%) | | |
| | **focal** | 36(51.4%) | | |
| | **unclassified** | 2(2.9%) | | |
| pathological MRI | | 19(27.1%) | | |
| number of AEDs | **1** | 44(62.9%) | | |
| | **2** | 12(17.1%) | | |
| | **≥3** | 14(20%) | | |
| total AEDs | **1** | 32(45.7%) | | |
| | **2** | 12(17.1%) | | |
| | **≥3** | 26(37.1%) | | |
| type of AEDs | **valproate** | 27(38.6%) | | |
| | **levetiracetam** | 23(32.9%) | | |
| | **carbamazepine** | 8(11.4%) | | |
| | **lamotrigine** | 13(18.6%) | | |
| | **oxcarbazepine/ eslicarbazepine** | 10(14.3%) | | |
| | **topiramate** | 9(12.9%) | | |
| | **lacosamide** | 7(10%) | | |
| | **zonisamide** | 3(4.3%) | | |
| | **phenytoin** | 3(4.3%) | | |
| | **phenobarbital** | 2(2.9%) | | |
| | **clobazam** | 3(4.3%) | | |
| mood stabilizers | | 49(70%) | | |
| AEP score | | 38.16 ± 11.64 | | |

PWE = patients with epilepsy, AEDs = Antiepileptic drugs, AEP = Adverse event profile.

**Table 2**
PHQ-9 score, MDD frequency, previously undiagnosed MDD and the four domains of QoL score in patients and controls.

| | PWE | controls | |
|---|---|---|---|
| PHQ-9 score | 7.57 ± 6.31 | 4.15 ± 4.13 | p < .001 |
| MDD presence | 20(28.5%) | 2(2.9%) | p < .001 |
| MDD undiagnosed | 8(40%) | 0 | – |
| physical health QoL | 61.61 ± 19.34 | 76.2 ± 14.05 | p < .001 |
| psychological QoL | 62.56 ± 19.49 | 69.9 ± 14.57 | p = .012 |
| social relations QoL | 70.36 ± 20.64 | 76.55 ± 15.3 | p = .046 |
| environment QoL | 65.4 ± 13.21 | 62.81 ± 11.7 | p > .05 |

PWE = patients with epilepsy, MDD = major depression disorder, QoL = quality of life.

[37].Regarding epilepsy characteristics, seizure frequency has been found to be strongly associated with depression [36,41]. Polypharmacy has been suggested as a risk factor for depression in epilepsy [39], although there are also studies that have not confirmed it [36,37]. Some AEDs may have negative effects on the mood and others have a mood stabilizing effect. Depression could be induced by different mechanisms, such as potentiation of GABA neurotransmission, folate deficiency, pharmacodynamic interactions with other AEDs and forced normalization. A previous psychiatric illness history is a risk factor for depression induction [42,43]. Furthermore, the adverse effects of AEDs have been found strongly associated to depression in patients with epilepsy [11,44–46].

Comparing our results with the literature, MDD was detected in a higher percentage of patients with epilepsy compared to previous studies, although controls had a similar incidence of MDD with the global general population [35]. These findings could potentially be explained by the financial crisis, if we accept that patients of chronic illnesses may be more vulnerable to socio-economic changes. In our series, depression was undiagnosed in 40% of patients with epilepsy and depression, while this proportion has been described in the literature to be higher than 60% [47,48].

Our results are in accordance with previous studies reporting that the adverse effects of AEDs play a major role in the incidence of depression [41].

### 4.2. Quality of life

Our patients had poorer physical health, psychological and social relationships, but their environment-related QoL was not different compared to healthy controls. The level of education of patients with epilepsy was associated with their physical health related QoL. The adverse effects of AEDs and the presence of depression were the factors that considerably influenced the QoL in patients.

Previous studies have reported that patients with epilepsy have a lower QoL compared to healthy controls [28,49,50]. In patients with epilepsy, their age and gender does not show any significant impact on QoL [17]. However, the higher the education level of the patients with epilepsy, the better their quality of life seems to be [51,52]. The role of

**Table 3**
Correlations of demographic and epilepsy characteristics with depression (PHQ-9 score) and quality of life (physical health, psychological, social relationships and environment-related quality of life).

| | phq-9 | Physical health | psychological | social | environment |
|---|---|---|---|---|---|
| age | ns | r = -.308, p = .009 | ns | ns | r = -.255, p = .033 |
| gender | ns | Ns | ns | ns | ns |
| education | ns | $r_s$ = .347, p = .003* | ns | ns | $r_s$ = .260, p = .029 |
| marital status | ns | ns | ns | ns | r = .312, p = .010 |
| age at epilepsy onset | ns | ns | ns | ns | ns |
| epilepsy duration | ns | r = -.247, p = .039 | ns | ns | ns |
| seizure frequency | $r_s$ = .241, p = .044 | $r_s$ = -.293, p = .014 | ns | ns | ns |
| epilepsy type | ns | Ns | ns | r = .310, p = .014 | ns |
| MRI findings | ns | Ns | ns | r = .412, p = .033 | ns |
| AEDs number | ns | r = -.268, p = .025 | ns | ns | ns |
| total AEDs | ns | r = -.267, p = .025 | ns | ns | ns |
| mood stabilizer AEDs | ns | Ns | ns | ns | ns |
| AEP score | r = .609, p < .001* | r = -.613, p < .001* | r = -.56, p < .001* | r = -.32, p = .007 | r = -.465, p < .001* |
| PHQ-9 | – | r = -.557, p < .001* | r = -.668, p < .001* | r = -.402, p = .001* | r = -.52, p < .001* |

ns = non-significant with p > .05, AEDs = Antiepileptic drugs, AEP = Adverse event profile.
* = significant after Bonferroni correction.

**Table 4**
Regression Analyses of QoL Domains.

| Physical health QoL | model 1 | model 2 | model 3 |
|---|---|---|---|
| age | −.217 | −.192 | −.157 |
| education | .262* | .159 | .110 |
| duration of epilepsy | | .055 | −.005 |
| seizure frequency | | −.004 | .04 |
| number of AEDs | | −.077 | −.113 |
| total AEDs | | −.100 | −.101 |
| AEP | | −.526*** | −.367** |
| PHQ-9 | | | −.279* |
| *Adjusted $R^2$ of model* | .130 | .418 | .458 |
| *$R^2$change* | .155 | .322 | .043 |
| *F change* | 6.17(2,67)** | 7.63(5,62)*** | 5.5(1,61)* |
| Psychological QoL | **model 1** | **model 2** | **model 3** |
| AEP | | −.560*** | −.244* |
| PHQ-9 | | | −.519*** |
| *Adjusted $R^2$ of model* | | .304 | .448 |
| *$R^2$change* | | .314 | .169 |
| *F change* | | 31.1(1,68)*** | 21.96(1,67)*** |
| *Social QoL* | **model 1** | **model 2** | **model 3** |
| type of epilepsy | | −.058 | −.074 |
| MRI findings | | −.294* | −.269* |
| AEP | | −.332** | −.146 |
| PHQ-9 | | | −.306* |
| *Adjusted $R^2$ of model* | | .169 | .218 |
| *$R^2$change* | | .205 | .058 |
| *F change* | | 5.67(3,66)** | 5.16(1,65)* |
| Environment QoL | **model 1** | **model2** | **model 3** |
| age | −.089 | −.102 | −.093 |
| education | .169 | .100 | .054 |
| marital status | −.22 | −.139 | −.146 |
| AEP | | −.401** | −.195 |
| PHQ-9 | | | −.353** |
| *Adjusted $R^2$ of model* | .089 | .234 | .304 |
| *$R^2$change* | .129 | .149 | .076 |
| *F change* | 7.54(1,64)* | 13.42(1,65)** | 7.54(1,64)** |

AEP = Adverse event profile questionnaire, QoL = quality of life.
* = p < .05.
** = p < .01.
*** = p < .001.

marital status in quality of life is controversial [17,40].

With regards to epilepsy characteristics, the duration of epilepsy has been reported to be both related [51] and unrelated [12] to quality of life. However, it is widely accepted that seizure frequency considerably affects patients' QoL [31,41,52,53], as long as polypharmacy has been found to be associated with poorer QoL [13,16,52,53]. Furthermore, the adverse effects of AEDs play a major negative role in QoL modulation [14,45,54,55]. The strong association between the presence of depression and the QoL in patients with epilepsy has already been established [12,13,16,42,44,45,56]. Previous studies have indicated that psychological factors, especially depression were more important predictors of a patients' quality of life, compared to epilepsy characteristics [30,31,57].

Consistent with previous authors [28,49,50], our patients with epilepsy had poorer QoL compared to controls, although the difference between patients and controls in domain scores was not as high as those reported in a study in Nairobi [28], where the same questionnaire was used.

Our study underlines that the level of education, a modifiable factor, is related to better QoL in epilepsy, also suggesting that the adverse effects of AEDs and depression seem to be much more powerful predictors of patients' QoL compared to demographics and all other epilepsy characteristics.

We acknowledge small sample size as a major limitation in the present study, as this is a single-center study. To assess the QoL, we used the World Health Organization WHOQOL-BREF questionnaire and not one typically used in epilepsy. Although not typically used, the WHOQOL-BREF is ideal for the comparison of QoL in patients with epilepsy and in healthy controls.

The absence of the AED type (mood stabilizers vs non-stabilizers) in relation with depression and QoL could be biased, since the AEDs were not administered at random, as the patient's psychological profile was intentionally taken into account for every therapeutic schema decision.

Larger studies, predominantly prospective, are needed to further elucidate factors which influence and improve the QoL in patients with epilepsy compared to healthy controls.

## 5. Conclusions

Patients with epilepsy have higher rates of depression compared to healthy controls, in Northwest Greece and is higher than reported in patients with epilepsy.

The adverse effects of AEDs are associated with depression in our study.

Patients with epilepsy in Northwest Greece have poorer physical health, psychological and socially - related QoL compared to healthy controls. The adverse effects of AEDs and depression are the most powerful predictors of a patient's QoL compared to demographics and other characteristics of epilepsy.

## Conflicts of interest

None.

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