Determinants of quality of life in patients with drug-resistant focal epilepsy

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ABSTRACT

Introduction: Focal drug-resistant epilepsy (DRE) has been associated with a significant burden of psychiatric comorbidity and low health-related quality of life (HRQoL). There is ample disagreement in previous studies as to which factors decisively influence HRQoL in this population. Here, we sought to assess the relationship between sociodemographic factors, epilepsy-related variables, and psychiatric comorbidity with HRQoL in a well-defined group of patients with focal DRE.
Methods: We consecutively recruited a sample of adult patients with confirmed focal DRE being considered for epilepsy surgery in a reference center in Lisbon, Portugal. Psychiatric diagnoses were defined according to the Mini-International Neuropsychiatric Interview (M.I.N.I.), and HRQoL was measured using the Quality-of-Life in Epilepsy Inventory (QOLIE-31). Associations with QOLIE-31 total score were tested using regression models.
Results: Among the forty patients included in the study, being diagnosed with a mood disorder was significantly associated with a lower total QOLIE-31 score ($\beta = -21.18$, p = 0.001) in univariate analysis. Multivariate analysis additionally identified female gender as a second determinant of lower HRQoL ($\beta = -21.22$, p = 0.001 for being diagnosed with a mood disorder; $\beta = -8.98$, p = 0.048 for female gender; adjusted $R^2 = 0.290$). Sociodemographic and epilepsy-related variables were not associated with HRQoL.
Conclusions: In our sample of adult patients with focal DRE, female gender and being diagnosed with a mood disorder were the only factors significantly associated with a poorer HRQoL. While clinical care often focuses on seizure control, epilepsy-related factors such as seizure frequency were not shown to have a significant influence on HRQoL. We suggest that an early comprehensive psychiatric evaluation and intervention can help improve HRQoL in these patients.

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1. Introduction

Approximately one-third of patients with epilepsy are not able to achieve adequate seizure control despite optimal medical treatment, and can, therefore, be classified as having drug-resistant epilepsy (DRE) [1]. Patients with focal epilepsy, in particular, are more likely to become drug-resistant [2]. Poor seizure control has been associated with higher mortality [3], cognitive deficits, educational and occupational underachievement, and social maladjustment [4]. The resulting burden of illness is associated with significant loss of health-related quality of life (HRQoL) [5,6], a dimension that is increasingly recognized as central in the treatment and rehabilitation of patients with epilepsy [7,8].

Despite the importance of HRQoL, to date, few studies have addressed its determinants in patients with focal DRE. Furthermore, the few existing studies have used very different case ascertainment strategies and have for the most part relied on unspecific instruments to measure HRQoL [9]. There is thus ample disagreement as to which factors decisively influence HRQoL in this population. While a few studies emphasized epilepsy-related factors such as seizure frequency [10–12] and seizure focus location [10,13], others have highlighted the importance of comorbid psychiatric symptoms such as depression [11,14,15], anxiety [13], suicidal ideation [16], or the presence of a personality disorder [12]. The role of psychiatric comorbidity has been emphasized in several studies, yet not all have included a comprehensive psychopathological assessment as part of their protocol [10] or used adequate assessment

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instruments, namely structured diagnostic interviews or rating scales [11,13–15].

The primary objective of this study was to analyze the relationship between sociodemographic factors, epilepsy-related variables, psychiatric comorbidity and HRQoL in a well-defined group of patients with focal DRE.

2. Methods

2.1. Sample

Adult patients with confirmed focal DRE referred to our Refractory Epilepsy Centre at Centro Hospitalar de Lisboa Ocidental, in Lisbon, Portugal, were recruited consecutively between January 2014 and July 2017. Drug-resistant epilepsy was defined as a failure of two tolerated antiepileptic drug (AED) schedules to achieve a seizure-free period of at least three times the longest pretreatment interseizure interval [17]. Furthermore, the drugs had to be adequate to the patient's specific type of epilepsy, and noncompliance excluded to a reasonable degree. Diagnosis of DRE and seizure focus localization were determined, for all patients, by a complete medical history, seizure phenomenology, neurological examination, and interictal and ictal video electroencephalogram (EEG) analyses, carried out by neurologists and neurophysiologists with expertise in epilepsy. Structural neuropathology was assessed by 3-T brain MRI (magnetic resonance imaging). All patients underwent formal, structured psychiatric and neuropsychological assessment as part of their routine presurgical evaluation. Patients with multifocal seizures, generalized interictal spikes, or marked cognitive impairment (IQ [intelligence quotient] lower than 70 in formal neuropsychological assessment) were not included in the current analysis. The study was conducted according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, and the local Ethics Committee approved the study protocol.

2.2. Sociodemographic and clinical data

We extracted sociodemographic data, such as age, gender, years of formal education, employment status, and marital status (married or equivalent/single), from the patient's records and registered them in an anonymized database. The following epilepsy-related factors were also registered: age of epilepsy onset, time interval between epilepsy onset and the current evaluation, the number of seizures in the previous month, number of AEDs currently prescribed, and seizure focus location (frontal, temporal, parietal, or occipital) and lateralization (right/left hemisphere).

2.3. Psychiatric assessment

All patients were assessed by a psychiatrist with experience in diagnosing and treating neuropsychiatric comorbidity in epilepsy (BS, AV, AJOM, or BBC). Psychiatric evaluation was blind to patient-reported HRQoL at the time of assessment. We established psychiatric diagnoses with the Portuguese language version [18] of the Mini-International Neuropsychiatric Interview (M.I.N.I.) [19]. This is a widely used and well-studied structured interview for psychiatric diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria, that has been validated against the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders diagnoses [20], as well as expert opinion [21]. We clustered all the diagnoses into the following eight diagnostic groups: 1) mood disorders, 2) anxiety disorders, 3) psychoactive substance use disorders, 4) psychotic disorders, 5) eating disorders, 6) somatoform disorders, 7) suicidality, and 8) adjustment disorders.

2.4. HRQoL

We assessed HRQoL with the Portuguese language version [22] of The Quality-of-Life in Epilepsy Inventory (QOLIE-31) [23], a widely used, self-rated questionnaire for the measurement of HRQoL in patients with epilepsy. It comprises a total of 31 items grouped into the following seven multi-item subscales: seizure worry, emotional well-being, energy/fatigue, cognitive function, medication effects, and social function. It also includes a single item that assesses overall HRQoL. This instrument produces scores from 0 to 100, with higher scores reflecting better HRQoL. A total score can be derived by weighting and summing each subscale scores.

2.5. Statistical analysis

We used the IBM Statistical Package for the Social Sciences version 23 and R version 3.5.1 for descriptive and inferential analysis. We described categorical variables using absolute values and percentages, and continuous variables as mean $\pm$ standard deviation. Statistical significance was set at a p-value lower than 0.05 in all tests. Since QOLIE-31 total scores showed a normal distribution (Kolmogorov–Smirnov test), we used linear regression to study their association with the independent variables. Independent variables with a p-value equal or smaller than 0.1 in univariate analysis were included in a multivariate linear regression model to determine their contribution to QOLIE-31 scores. Variables that improved model fit and were significant (p-value < 0.1) in the multivariate model were retained using the backward method. Model fit was assessed using R^2.

3. Results

3.1. Sociodemographic and clinical characteristics of the sample

A total of forty patients with focal DRE were eligible for inclusion in this study. The distribution of sociodemographic and epilepsy-related variables in the sample is detailed in Table 1.

There was considerable variability in seizure frequency in our sample, with reported seizures in the previous month ranging from 0 to 90, with a median of 2 seizures. Nineteen patients were taking an association of 2 AEDs, 12 were taking 3, and 2 were taking 4 AEDs. Seven patients were taking only one AED. Twenty-one patients had radiological findings compatible with mesial temporal sclerosis. Other pathologies described in brain MRI reports were as follows: tumors (5), focal cortical dysplasias (4), blood vessel malformations (2), and brain abscess (1). Seven patients showed no structural pathology on brain MRI.

Table 2 shows the psychiatric diagnoses based on the M.I.N.I., with 23 patients (57.5%) diagnosed with at least one psychiatric disorder. Table 3 shows the mean scores for each of the QOLIE-31 subscales and for the total score.

Table 1
Sociodemographic and epilepsy-related characteristics of the sample. Values are means $\pm$ standard deviation or absolute numbers (percentage of the total sample).

Variable	Total ($N = 40$)
Age (years)	38.83 ± 12.01
Male gender	17 (42.5%)
Years of formal education	10.82 ± 3.68
Employed	24 (60%)
Married or equivalent	15 (37.5%)
Age (years) at epilepsy onset	18.07 ± 12.13
Epilepsy duration (years)	20.75 ± 14.09
Number of seizures in the previous month	8.43 ± 20.45
Number of AEDs currently prescribed	2.22 ± 0.8
Seizure focus location:	
Frontal lobe	9 (22.5%)
Temporal lobe	31 (77.5%)
Seizure focus side, right hemisphere	21 (52.5%)

Table 2

Prevalence of psychiatric disorders. Values are absolute numbers (percentage of the total sample).

Diagnostic groups	Diagnoses	N (%), (total N = 40)
Mood disorders		7 (17.5%)
	Major depressive episode	6 (15%)
	Major depressive episode + past hypomanic episode	1 (2.5%)
Anxiety disorders		16 (40%)
	Panic disorder	6 (15%)
	Agoraphobia	4 (10%)
	Social phobia	6 (15%)
	Obsessive–compulsive disorder	1 (2.5%)
	Generalized anxiety disorder	7 (17.5%)
Psychoactive substance use disorders	Alcohol dependence	1 (2.5%)
Psychotic disorders	Psychotic disorder	4 (10%)
Suicide risk		3 (7.5%)
	Low risk	1 (2.5%)
	High risk	2 (5%)
Adjustment disorders	Adjustment disorder	3 (7.5%)

Table 4

Factors influencing HRQoL.

Variable	β	SE β	Standardized β	p
Gender (m/f)	−8,928	5,080	−0,274	0,087*
Age	0,273	0,216	0,202	0,212
Employment (y/n)	6,132	5,237	0,187	0,249
Education	2,493	2,365	0,169	0,299
Married or equivalent (y/n)	7,166	5,267	0,216	0,182
Epilepsy onset <18 years (y/n)	0,826	5,329	0,025	0,878
Epilepsy duration	0,206	0,185	0,178	0,270
Seizure frequency	−0,210	0,125	−0,264	0,100*
No. of AED	−1,012	3,301	−0,050	0,761
Seizure focus (FLE/TLE)	−6,166	6,173	−0,160	0,324
Seizure focus (right/left)	−2,504	5,214	−0,078	0,634
Any psychiatric diagnosis (y/n)	−7,198	5,152	−0,221	0,170
Mood disorders (y/n)	−21,180	5,952	−0,500	0,001**
Anxiety disorders (y/n)	−4,345	5,284	−0,132	0,416
Psychotic disorders (y/n)	−1,414	8,702	−0,026	0,872
Adjustment disorders (y/n)	−3,915	9,894	−0,064	0,695
Suicide risk (y/n)	4,809	9,884	0,079	0,629

Presented values are beta (β) coefficients and standard error of the β coefficient (SE β), standardized β coefficients, and p values of the β coefficients from simple linear regression using the QOLIE-31 total score as the dependent variable. Asterisks indicate p-values associated with each beta coefficient as follows: ** = $p < 0.05$, * = $p < 0.1$.
Legend: AED: antiepileptic drugs; FLE: frontal lobe epilepsy; TLE: temporal lobe epilepsy.

3.2. Factors influencing HRQoL

Table 4 summarizes the simple regression models for the QOLIE-31 total score as the dependent variable, using each of the sociodemographic and clinical measures as the independent variables. We found a statistically significant association between the QOLIE-31 total score and being diagnosed with a mood disorder (F = 12.661 with p = 0.001, β = −21.18 with p = 0.001), showing that having a mood disorder was associated with having lower values of the QOLIE-31 overall score. The model fit for the data was modest (adjusted R^2 = 0.23). No other sociodemographic or epilepsy-related variable showed a statistically significant association with the QOLIE-31 total score in univariate analysis.

We then performed a multiple linear regression model, again with the QOLIE-31 total score as the dependent variable, and including all variables with p ≤ 0.1 in univariate regression as the predictors in the initial model. The initial multivariate linear regression model thus included diagnosis of a mood disorder, gender, and the number of seizures in the past month as independent variables. The single patient with a diagnosis of a psychoactive substance use disorder was removed from the analysis, because its presence did not affect the results but did affect assumptions of the model. Variables with an associated p-value of less than 0.1 were selected using the backward method. The final model included only diagnosis of a mood disorder and gender as independent variables (β = −21.22, p = 0.001 and β = −8.98, p = 0.048, respectively; F = 8.948 with p = 0.001, adjusted R^2 = 0.29). Both independent variables had negative β coefficients, showing that the QOLIE-31 total score was lower in the presence of a mood disorder and in female patients. Multicollinearity tests suggested that the two predictors are independent, with an average variance inflation factor = 1.00001. The multiple regression model showed an improvement of model fit

compared to the simple regression model that only included diagnosis of a mood disorder as the predictor (adjusted R^2 improved from 0.23 to 0.290, F for change in R^2 = 4.177, p = 0.048) (Table 5).

4. Discussion

Our objective was to identify clinical determinants of HRQoL in patients with focal DRE. To achieve this, we assessed a cohort of 40 patients with focal DRE using a combination of structured clinical assessment instruments. We found that, in this cohort of patients with focal DRE, being diagnosed with a mood disorder was the only statistically significant determinant of poorer HRQoL in univariate analysis. Multivariate analysis additionally identified female gender as a second determinant of lower HRQoL. Our results are in line with previous studies that have identified depression as the most robust determinant of quality of life in patients with focal DRE [11,14,15,24]. No epilepsy-related factor was shown to be significantly associated with HRQoL in our study. This finding contrasts with previous studies that highlighted seizure frequency as a major determinant of QOLIE-31 scores in patients with focal DRE [6,10]. With regard to gender differences in self-reporting of quality of life, one previous study [25] noted that female patients scored lower in general health self-assessment across several European countries. The reasons behind this gender difference remain unclear and constitute a clear area in need of more research within the context of other health-related gender inequalities [26].

The high prevalence of psychiatric disorders in our sample (57.5%) is also worthy of note, with anxiety disorders being the most common diagnoses and 40% of patients meeting criteria for at least one anxiety disorder. Patients often develop anxiety after being diagnosed with epilepsy, or after experiencing a seizure for the first time. The uncertainty of when and where a seizure can occur, often without warning, can be a major cause of anxiety for many patients. Some patients also become anxious about social rejection because of their condition – for instance, being discriminated at work. It is also interesting to note that despite being the most prevalent disorder in this group, anxiety was not identified as a significant predictor of HRQoL. It has been reported that anxiety and depression impact differently on quality of life, with depression accounting for a higher proportion of variance as a predictor of HRQoL [27].

These figures also suggest that the prevalence of mental disorders in patients with focal DRE may be higher than previously reported by studies that relied on unstructured clinical assessments for psychiatric diagnosis. Our findings illustrate the crucial importance of using structured

Table 3

Mean QOLIE-31 subscale scores. Values are means (standard deviation).

Subscale	Mean ± SD, (N = 40)
Overall HRQoL	59.19 ± 17.31
Seizure worry	41.54 ± 27.33
Emotional well-being	59.85 ± 20.96
Energy/fatigue	50.50 ± 17.01
Cognitive function	51.20 ± 25.66
Medication effects	45.77 ± 30.09
Social function	58.63 ± 23.78
Total score	54.73 ± 16.30

Table 5
Summary of multivariate regression analysis for variables associated with QOLIE-31 total score.

Variable	Model 1				Model 2			
	β	SE β	St. β	p	β	SE β	St. β	p
Mood disorders (y/n)	−20,342	6,038	−0,480	0,002**	−21,219	5,718	−0,501	0,001**
Gender (m/f)	−8,480	4,553	−0,260	0,071*	−8,983	4,395	−0,276	0,048**
Seizure frequency	−0,058	0,116	−0,073	0,621				
Adjusted R^2	0,275				0,290			
F for change in R^2	5,928**				0,249			

Presented values are beta (β) coefficients and standard error of the β coefficient (SE β), standardized β coefficients, and p values of the β coefficients from multivariate linear regression using the QOLIE-31 total score as the dependent variable. Adjusted R^2 and F statistics for change in R^2 are also present. Asterisks indicate p-values as follows: ** = $p < 0.05$, * = $p < 0.1$.

psychiatric assessment tools in this context for diagnosing common mental health problems that will otherwise remain unrecognized and untreated. In the presence of a major, chronically incapacitating neurological disorder such as epilepsy relevant comorbid psychopathology may pass undetected or be insufficiently valued by the assessing clinician, and adopting a systematic approach based on well-validated, structured assessment tools may help to overcome these difficulties. This is particular important in view of evidence showing that comorbid depression in epilepsy is associated with worse treatment compliance and increased risk of seizures [28].

The main strengths of this study are its well-defined clinical sample, the comprehensive psychiatric assessment based on a well-validated interview schedule, and the evaluation of HRQoL based on an assessment instrument that has been specifically designed and validated for patients with epilepsy. There are, however, several limitations. Recruitment in a single institution may limit the generalizability of the main findings. The sample size was small, with consequent loss of statistical power. Our regression models showed only a modest model fit for the data, which suggests that other determinants of HRQoL and psychiatric comorbidity are at play. Future research should thus refine the methodology of the present study. The preferred design should be prospective and include a comparison between DRE patients and a control group with other chronic neurological illnesses. Finally, it would be interesting to determine if treating mental disorders in this population would lead to a measurable improvement in HRQoL.

In conclusion, our study shows that being diagnosed with a mood disorder and female gender are associated with a lower HRQoL in patients with focal DRE. While clinical care often focuses on seizure control, epilepsy-related factors such as seizure frequency were not shown to have a significant influence on HRQoL in our sample. We thus recommend that patients with focal DRE be offered an early comprehensive psychiatric evaluation for timely diagnosis and treatment of comorbid mental disorders, possibly contributing to a timelier recovery of quality of life in this population.

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Declaration of competing interest

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References

[1] Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry. 2004;75:1376–81.

[2] Picot MC, Baldy-Moulinier M, Daures JP, Dujols P, Crespel A. The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. Epilepsia. 2008;49:1230–8.

[3] Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. N Engl J Med. 2010;363:2522–9.

[4] Laxer KD, Trinka E, Hirsch LJ, Cendes F, Langfitt J, Delanty N, et al. The consequences of refractory epilepsy and its treatment. Epilepsy Behav. 2014;37:59–70. https://doi.org/10.1016/j.yebeh.2014.05.031 [Epub 2014 Jun 27].

[5] Cramer JA. Quality of life for people with epilepsy. Neurol Clin. 1994;12:1–13.

[6] Jacoby A, Baker GA. Quality-of-life trajectories in epilepsy: a review of the literature. Epilepsy Behav. 2008;12:557–71.

[7] Leppik IE. Quality of life of people with epilepsy in the United States. Clin Ther. 1998; 20(Suppl A):A13–8 [discussion A58-60].

[8] Vickrey BG, Hays RD, Graber J, Rausch R, Engel Jr J, Brook RH. A health-related quality of life instrument for patients evaluated for epilepsy surgery. Med Care. 1992;30: 299–319.

[9] Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. Epilepsia. 2011;52:2168–80. https://doi.org/10.1111/j.1528-1167.2011.03213.x [Epub 2011 Aug 29].

[10] Alonso-Vanegas MA, Cisneros-Franco JM, Castillo-Montoya C, Martinez-Rosas AR, Gomez-Perez ME, Rubio-Donnadieu F. Self-reported quality of life in pharmacoresistant temporal lobe epilepsy: correlation with clinical variables and memory evaluation. Epileptic Disord. 2013;15:263–71.

[11] Elsharkawy AE, Thorbecke R, Ebner A, May TW. Determinants of quality of life in patients with refractory focal epilepsy who were not eligible for surgery or who rejected surgery. Epilepsy Behav. 2012;24:249–55.

[12] Pauli C, Thais ME, Claudino LS, Bicalho MA, Bastos AC, Guarnieri R, et al. Predictors of quality of life in patients with refractory mesial temporal lobe epilepsy. Epilepsy Behav. 2012;25:208–13.

[13] Andelman F, Fried I, Neufeld MY. Quality of life self-assessment as a function of lateralization of lesion in candidates for epilepsy surgery. Epilepsia. 2001;42: 549–55.

[14] Garcia ME, Garcia-Morales I, Gil-Nagel A. Prevalence of depressive symptoms and their impact on quality of life in patients with drug-resistant focal epilepsy (IMDYVA study). Epilepsy Res. 2015;110:157–65.

[15] Meldolesi GN, Picardi A, Quarato PP, Grammaldo LG, Esposito V, Mascia A, et al. Factors associated with generic and disease-specific quality of life in temporal lobe epilepsy. Epilepsy Res. 2006;69:135–46.

[16] Andrade-Machado R, Ochoa-Urrea M, Garcia-Espinosa A, Benjumea-Cuartas V, Santos-Santos A. Suicidal risk, affective dysphoric disorders, and quality-of-life perception in patients with focal refractory epilepsy. Epilepsy Behav. 2015;45:254–60.

[17] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on therapeutic strategies. Epilepsia. 2010;51:1069–77.

[18] Amorim P. Mini International Neuropsychiatric Interview (MINI): validação de entrevista breve para diagnóstico de transtornos mentais. Rev Bras Psiquiatr. 2000;22:106–15.

[19] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(Suppl. 20):22–33 [quiz 34-57].

[20] Sheehan DV, Lecrubier Y, Harnett Sheehan K, Janavs J, Weiller E, Keskiner A, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry. 1997;12:232–41.

[21] Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry. 1997; 12:224–31.

[22] da Silva TI, Ciconelli RM, Alonso NB, Azevedo AM, Westphal-Guitti AC, Pascalicchio TF, et al. Validity and reliability of the Portuguese version of the quality of life in epilepsy inventory (QOLIE-31) for Brazil. Epilepsy Behav. 2007;10:234–41 [Epub 2007 Feb 9].

[23] Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia. 1998;39:81–8.

[24] Luoni C, Bisulli F, Canevini MP, De Sarro G, Fattore C, Galimberti CA, et al. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. Epilepsia. 2011;52:2181–91.

[25] Buck D, Jacoby A, Baker GA, Ley H, Steen N. Cross-cultural differences in health-related quality of life of people with epilepsy: findings from a European study. Qual Life Res. 1999;8:675–85.
[26] Ashwin M, Rakesh PS, Pricilla RA, Manjunath K, Jacob KS, Prasad J. Determinants of quality of life among people with epilepsy attending a secondary care rural hospital in south India. J Neurosci Rural Pract. 2013;4:S62–6.
[27] Cramer JA, Brandenburg N, Xu X. Differentiating anxiety and depression symptoms in patients with partial epilepsy. Epilepsy Behav. 2005;6:563–9.
[28] Ettinger AB, Good MB, Manjunath R, Edward Faught R, Bancroft T. The relationship of depression to antiepileptic drug adherence and quality of life in epilepsy. Epilepsy Behav. 2014;36:138–43.