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Original Article

Psychiatric comorbidity and quality of life in patients with epilepsy on anti-epileptic monotherapy and polytherapy

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Abstract

Objective: The bio-psycho-social factors affecting the quality of life in patients with epilepsy can be numerous but are often overlooked. The behavioral side effects of anti-seizure medications can be one such potential factor. The aim of the study is to address the effect of the number of anti-seizure medications on the development of psychiatric comorbidity and quality of life in patients with adequate seizure control. **Materials and Methods:** The study recruited 100 participants with generalized tonic-clonic seizures from a tertiary care center in North India, who were seizure-free from the last 1 month. The study participants were divided into two groups based on whether they were on monotherapy or polytherapy. The two groups were matched for their socio-demographic and clinical profile. We assessed for psychiatric comorbidity in each group using Mini International Neuropsychiatric Interview. All the study participants were given Hindi translated version of quality of life in the epilepsy-31 questionnaire for objective assessment of the quality of life. **Results:** The patients receiving anti-epileptic polytherapy had significantly higher prevalence of psychiatric comorbidity than patients on monotherapy. Furthermore, the patients on polytherapy scored significantly less on the cognitive domain of quality of life as well as the overall quality of life domain in the epilepsy-31 questionnaire. **Conclusion:** The patients with epilepsy must be evaluated for psychiatric comorbidity and side effect profile of anti-seizure medications to improve the quality of life. This is particularly more important for patients who are on anti-epileptic polytherapy even if the seizure control is adequate.

Keywords: *Epilepsy, Psychiatric comorbidity, Quality of life*

Introduction

Epilepsy is a chronic neurological condition characterized by recurrent unprovoked seizures. The estimated median lifetime prevalence of epilepsy in developed nations is 5.8/1000. In developing nations the prevalence of epilepsy is 15.4/1000 for rural and 10.3/1000 for the urban population [1]. Globally, epilepsy is among top five neurological disorders in terms of age-standardized disability adjusted life years (DALYs). DALYs from epilepsy were highest in people aged 5 to 29 years as per the Global Burden of Disease Study, 2016 [2]. Furthermore, in developing countries like India, there is a lack of awareness about the nature of the illness, the presence of stigma, and huge treatment gap which further adds to the burden of epilepsy in these nations [3-5]. Apart from the neurological dysfunction, patients with epilepsy have various comorbid psychological and psychosocial issues that predispose them to various psychiatric disorders [6-8]. It has been well established that the prevalence of psychiatric disorders is higher among patients with epilepsy than among the general population [9]. Furthermore, it has been observed that addressing psychiatric comorbidity improved the quality of life in patients with epilepsy who had adequate seizure control [10].

The concept of "Quality of life" [11] thus provides a new dimension where the patient's point of view is assessed regarding the impact of disease and medical treatment. In this regard, comorbid psychiatric disorders significantly impair the quality of life in patients with epilepsy [12,13]. However, inadequate seizure control has been the single most important

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therapeutic target and various other factors predisposing to the psychiatric disorders are often underlooked in patients with epilepsy [14]. In our literature review we could find few studies done in the West [14,15] to assess factors responsible for the quality of life in patients with epilepsy apart from seizure control. However, there is the paucity of such studies in the Indian context.

It has been well known that anti-seizure medications have both positive as well as negative psychotropic effects [16-18]. It has been argued that cognitive side effects of anti-seizure medications, namely, psychomotor slowing [19], are frequently missed by clinicians. Thus the effects of anti-seizure medications can be considered as potentially important predictors of quality of life in patients with epilepsy. The present study is therefore aimed to address the contribution of anti-epileptic monotherapy and polytherapy to psychiatric comorbidity and quality of life in patients with epilepsy who were seizure-free for a certain period.

Materials and Methods

Study setting and design

The study was a cross-sectional study conducted in the outpatient department of Psychiatry and Neurology at Pt. B. D. Sharma PGIMS, Rohtak. The study received ethical clearance from the Institutional Ethics Committee (vide letter no. IEC/04). A written informed consent was obtained from each of the study participants. One hundred patients with generalized tonic-clonic seizures meeting the study criteria were recruited over a period of 1 year, ranging from January 2019 to December 2019. The participants were asked to fill the Self-administered Quality of Life in Epilepsy-31 questionnaire (QOLIE-31) [20].

Study procedure

Out of the one hundred participants, 50 patients who were on anti-epileptic "Monotherapy" constituted Group 1 and the rest 50 who were on "Polytherapy" constituted Group 2. To keep the two groups homogenous, patients with more than 18 years of age, having generalized tonic-clonic seizures and on stable doses of anti-seizure medications were included in the study.

The patients in the two groups were comparable in terms of seizure control and had been on regular follow up since the last 1 year. The presence of any other chronic medical illness, mental and behavioral disorders due to substance, intellectual disability, and speech or hearing disability constituted the exclusion criteria for the study.

The diagnosis of epilepsy was confirmed by the author S. D. following which detailed socio-demographic and clinical variables of the study participants were recorded in a self-designed form. Sociodemographic data included: age, sex, marital status, education level, and socioeconomic status. The clinical variables included: age of onset of epilepsy, total duration of epilepsy, duration from last seizure episode, anti-epileptic treatment, and history of comorbid medical, psychiatric, or substance use disorders.

Tools used

Mini International Neuropsychiatric Interview Version 6.0.0

The psychiatric comorbidity was assessed using the Mini International Neuropsychiatric Interview Version 6.0.0 [21]. It is a brief structured interview for screening and diagnosis of Major Axis 1 psychiatric disorders in DSM IV and ICD 10. This tool is developed jointly by clinicians and psychiatrists from United States and Europe. It can be administered by the clinicians in a small period which is approximately 15 min. Furthermore, MINI 6.0.0 overcomes the impediment of the two-stage interview process.

There are screening and diagnostic modules for 17 most common psychiatric diagnostic categories. The patient's verbal responses are recorded with the phrases "yes" or "no" in each module by the clinician. "Suicidality" is one of the modules which assesses the intent of harming oneself, active or passive death wishes and any plans for self-harm.

Quality of Life in Epilepsy-31 Version 1.0

The quality of life was assessed using the Self-administered QOLIE-31 Scale. QOLIE-31 is a validated instrument containing seven multi-item scales which include seizure worry, overall quality of life, emotional well-being, energy, cognitive, medication effects, and social function. It is a shorter version of the QOLIE-89 inventory and its Hindi translated version was used for the ease of study participants. QOLIE-31 questionnaire has been validated in Hindi [22,23]. The overall score range was 0–100. The higher the score the better will be the quality of life. Cronbach's alpha and intraclass correlation coefficients obtained for QOLIE-31 in the present study were 0.946 and 0.974, respectively, which indicated good internal consistency and reproducibility of the tool for assessment of QoL for the subjects of the present study.

Statistical analysis

Descriptive statistics including mean and standard deviation were calculated for continuous variables. Since the main goal of this study was to compare the effects of anti-epileptic mono-therapy and poly-therapy with regard to the prevalence of psychiatric comorbidity and quality of life in patients with epilepsy, Chi-square test on discrete data for psychiatric comorbidity, independent sample *t*-test, and analysis of variance for all domains of QOLIE-31 scale were performed. The *P* value specified for significance was < 0.05.

Results

One hundred patients with generalized tonic-clonic seizures enrolled for the study were divided into two groups based on the prescribed number of anti-seizure medications. The patients on single anti-seizure medication constituted Group I (Mono-therapy group) and the patients on two or more anti-seizure medications constituted Group II (Poly-therapy group).

Socio-demographic and clinical characteristics of the study groups

The socio-demographic and clinical profiles of the study groups are summarized in Table 1. The mean age of the study population was around 27.88 ± 8.51 years. The mean Body Mass Index among males was 25.24 ± 3.42 and among females 24.06 ± 4.42. The Mean age of onset of seizures in the study

Table 1: Comparison of Group I and Group II on sociodemographic variables using Chi-square test

Characteristics	Monotherapy Group I (*n*=50)	Polytherapy Group II (*n*=50)	χ^2	*P*
Age range (years)				
18-25	21	28	2.965	0.539
26-34	18	15		
35-44	8	5		
>45	3	2		
Sex				
Male	30	27	0.36	0.54
Female	20	23		
Marital status				
Unmarried	23	21	0.16	0.687
Married	27	29		
Education				
Illiterate	4	6	5.471	0.361
Upto 5th	9	13		
Upto 8th	9	13		
Upto 10th and 12th	10	8		
Graduation	13	9		
Postgraduation	5	1		
Employment status				
Unemployed	8	12	7.61	0.17
Full time employed	10	12		
Part time employed	7	10		
Self employed	8	9		
Student	9	6		
Homemaker	8	1		
Socioeconomic status				
Lower	26	32	1.477	0.22
Middle	24	18		
Age at onset of epilepsy				
5-10	3	5	1.813	0.770
11-15	10	12		
16-20	22	17		
21-25	3	5		
>25	12	12		
Total duration of epilepsy				
1-5	23	22	2.555	0.637
6-10	18	18		
11-15	5	7		
16-20	2	3		
>20	2	0		
Treatment				
Monotherapy	100	0	0.000	1.000
Polytherapy	0	100		

population was 20.73 ± 9.71 years. The mean total duration of epilepsy was 7.12 ± 4.98. The socioeconomic status was assessed using the Modified Kuppuswamy Socioeconomic grading scales with the income range of the year 2012 [24]. There was no significant difference in the sociodemographic profile of the two groups ($P > 0.05$).

Comparative analysis of scores on domains of Quality of Life in Epilepsy-31 scale between "age of onset of epilepsy" of the study population

One-way ANOVA or analysis of variance test was done to assess the difference of scores of various domains of QOLIE-31 scale, if any, among different age of onset categories of epilepsy of the study population. In none of the variables, the assumptions of the test were violated.

There was no statistically significant difference in any domain score among different age of onset categories as suggested by *P* value > 0.05 [Table 2].

Comparative analysis of scores on domains of Quality of Life in Epilepsy-31 scale between "Total duration of epilepsy" subgroups of the study population

One-way ANOVA or analysis of variance test was done to assess the difference of scores of various domains of QOLIE-31 scale, if any, among different "total duration of illness" subgroups of the study population. In none of the variables, the assumptions of the test were violated. Score on all the domains varied due to the total duration of epilepsy.

There was a significant main effect of the total duration of illness on the domains of energy/fatigue and cognitive functions [Table 3].

Psychiatric comorbidity among study groups

Out of 50 patients on Mono-therapy, 5 patients had major depressive disorder, 4 had anxiety spectrum disorders and 2 had suicidality. Out of 50 patients on Poly-therapy, 16 patients had major depressive disorder, 14 had anxiety spectrum disorders and 9 had suicidality. The use of Poly-therapy was significantly associated with psychiatric comorbidity with $P < 0.05$ [Table 4].

Psychiatric comorbidity and individual ASMs in the mono-therapy group

Out of 50 patients on Mono-therapy, there were 16 patients on Valproate out of which 7 had psychiatric comorbidity. Out of 14 patients on Phenytoin, 8 had psychiatric comorbidity and out of 20 patients on Levetiracetam, 8 had psychiatric comorbidity. However, there was no significant difference between the three anti-seizure medications ($P > 0.05$) [Table 5].

Quality of life in study groups

Score on all the domains on the QOLIE-31 scale varied due to differences in treatment type. The mean overall quality of life score in patients on anti-epileptic monotherapy was 59.78 ± 18.14. The mean overall quality of life score in patients on anti-epileptic polytherapy was 37.58 ± 18.45. The difference in overall quality of life was statistically significant (P value < 0.05). The difference in the two treatment type was also statistically significant on the domain of cognitive functions with $P < 0.05$ [Table 6].

Discussion

The study is one of a kind from a developing nation to assess the independent association of the number of anti-seizure medications with psychiatric comorbidity and quality of life in patients with epilepsy. The sociodemographic and clinical confounders were kept to the minimum in our study. In our study, we found a significant effect of the total duration of epilepsy on the domains of energy/fatigue and cognitive functions on the QOLIE-31 scale. The findings of Auriel *et al*. [14] are not consistent with our study findings.

Table 2: Comparative analysis of scores on domains of quality of life in epilepsy - 31 Scale between "age of onset of epilepsy" of the study population using one-way ANOVA

Variable	Source of variance	Sum of squares	df	Mean square (variance)	*F* ratio	*P*
Seizure worry	Between groups	2568.74	4	642.18 (589.25)	1.090	0.371
	Within groups	32408.82	55			
	Total	34977.57	59			
Emotional well being	Between groups	3925.23	4	981.30 (912.46)	1.075	0.378
	Within groups	50185.69	55			
	Total	54110.93	59			
Energy/ fatigue	Between groups	3374.75	4	848.68 (624.72)	1.359	0.260
	Within groups	34359.83	55			
	Total	37754.58	59			
Cognitive	Between groups	3685.49	4	921.37 (419.50)	2.196	0.081
	Within groups	23072.79	55			
	Total	26758.29	59			
Med effects	Between groups	1725.29	4	431.32 (641.89)	0.672	0.614
	Within groups	35304.21	55			
	Total	37029.51	59			
Social functioning	Between groups	814.23	4	203.56 (657.53)	0.310	0.870
	Within groups	36164.29	55			
	Total	36978.53	59			
Overall QoL	Between groups	651.65	4	162.91 (475.83)	0.342	0.848
	Within groups	26170.68	55			
	Total	26822.34	59			
Overall score	Between groups	1870.34	4	467.58 (407.54)	1.147	0.344
	Within groups	22414.75	55			
	Total	24285.10	59			

QoL: Quality of life

Table 3: Comparative analysis of scores on domains of quality of life in epilepsy - 31 Scale between "total duration of epilepsy" subgroups of the study population using one-way ANOVA

Variable	Source of variance	Sum of squares	df	Mean square (variance)	*P*
Seizure worry	Between groups	4186.63	4	1046.65 (559.83)	0.129
	Within groups	30790.93	55		
	Total	34977.57	59		
Emotional well being	Between groups	5928.75	4	1482.18 (876.04)	0.165
	Within groups	48182.18	55		
	Total	54110.93	59		
Energy/fatigue	Between groups	6242.14	4	1560.53 (572.95)	0.039
	Within groups	31512.44	55		
	Total	37754.58	59		
Cognitive	Between groups	4597.28	4	1149.32 (402.92)	0.032
	Within groups	22161.00	55		
	Total	26758.29	59		
Med effects	Between groups	3609.57	4	902.39 (607.63)	0.219
	Within groups	33419.93	55		
	Total	37029.51	59		
Social functioning	Between groups	2265.66	4	566.41 (631.14)	0.472
	Within groups	34712.87	55		
	Total	36978.53	59		
Overall QoL	Between groups	3534.65	4	883.66 (423.41)	0.095
	Within groups	23287.68	55		
	Total	26822.34	59		
Overall score	Between groups	3106.99	4	776.75 (385.05)	0.105
	Within groups	21178.10	55		
	Total	24285.10	59		

QoL: Quality of life

Although there was a trend of decreasing scores of QoL in those with longer duration in the study by Auriel *et al*., it was not significant. The prevalence of psychiatric comorbidity was 38% in patients on monotherapy as against 66% among

Table 4: Comparative analysis of psychiatric comorbidity among study groups using Chi-square test

Parameters	Monotherapy (*n*=50)	Polytherapy (*n*=50)	*P*
Major depressive disorder	5	16	0.028
Anxiety spectrum disorder	4	14	0.029
Suicidality	2	9	0.044

Table 5: Comparative analysis of psychiatric comorbidity and individual anti-seizure medication in the monotherapy group

Parameters	Valproate	Phenytoin	Levetiracetam	*P*
Major depressive disorder	1	2	4	0.256
Anxiety spectrum disorder	3	3	4	0.346
Suicidality	3	3	4	0.167

Table 6: Comparative analysis of scores on domains of quality of life in epilepsy - 31 Scale with treatment therapy using independent *t*-test

Variables	Mean±SD		*t*	*P*
	Mono-therapy	Poly-therapy		
Seizure worry	33.63±25.20	0.232±0.818	0.232	0.818
Emotional well being	56.73±29.03	0.243±0.809	0.243	0.809
Energy/fatigue	55.52±24.51	0.779±0.439	0.779	0.439
Cognitive function	51.06±21.02	2.509±0.015	2.509	0.015
Medication effects	52.84±27.50	1.653±0.104	1.653	0.104
Social functioning	46.46±27.83	0.582±0.563	0.582	0.563
Overall QoL	59.78±18.14	37.58±18.45	4.700	0.01

QoL: Quality of life, SD: Standard deviation

those on polytherapy. These findings are consistent with the findings of the study conducted by Vujisić *et al*. [25] in which prevalence of depression was 72.72% in patients on three or more anti-seizure medications as compared to only 15.38% among patients on monotherapy. The prevalence of depression, anxiety, and suicidality was significantly higher in patients on polytherapy ($P < 0.05$). The mechanism of anti-seizure medications could be associated with higher risk of depressive symptoms among those on polytherapy [26,27].

This significant difference in prevalence reinforces the findings from the previous studies [28,29]. In 2008 United States Food and Drug Administration had also alerted regarding the potential risk of suicidality due to anti-seizure medications [30]. The caution for suicidality appears to be more with newer anti-seizure medications as proposed by Andersonhn *et al*. in their study. There was more risk of depressive symptoms and self-harm with Levetiracetam than for the conventional anti-seizure medications, phenytoin, valproate, and carbamazepine [31]. However, in our study, there was no significant difference within the monotherapy group among different anti-seizure medications.

Our results further align with findings of another study by Auriel *et al*. [14] which supported side effects of anti-epileptic drugs monotherapy as an important factor responsible for the poor quality of life even in well-controlled epilepsy. The cognitive domain on the QOLIE-31 scale was significantly affected in patients on polytherapy ($P = 0.015$) in our study. The adverse effects of anti-seizure medications, cognitive deficits, in particular, are not surprising and the negative impact on quality of life is well established in the literature [32-34]. The common pathological mechanism [35] underlying epilepsy and depressive disorder further add to the cognitive decline in patients with epilepsy secondary to the affective state.

Therefore, it becomes empirical for the clinicians to give due consideration to various potential factors responsible for psychiatric comorbidity in epilepsy patients, in particular the effects of anti-seizure medications. It will promote adherence, seizure control, emotional well-being, and socio-occupational functioning. Our study thus addresses the direct role of the clinician with respect to the rational use of anti-seizure medications, detailed inquiry about the side-effects of anti-seizure medications along with symptoms of psychiatric disorders. Certain tools like the SIDAED questionnaire can be used to assess the patient-reported adverse effects of anti-seizure medications and their impact on the patient's outcome [36]. This will provide more accurate information of patients' concerns which, if timely addressed, can provide a better quality of life in patients with epilepsy.

Limitation of the study

The study was limited by the cross-sectional design. The other limitation is that the QOLIE-31 questionnaire does not provide an elaborative side effect profile of anti-seizure medications. Thus, the study does not take into account the detailed side effect profile of individual pharmacological agents. Moreover, the patients on anti-epileptic polytherapy may also have more negative experiences in terms of long duration of uncontrolled epilepsy and more severe disease that may be considered as confounding factors contributing to more psychiatric comorbidity in the polytherapy group.

Conclusion

The burden of epilepsy as well as treatment gap for epilepsy and psychiatric disorders is huge in developing nations. Anti-seizure medications are prescribed on long-term basis and hence have a higher potential to cause adverse drug reactions. Furthermore, they are known to cause cognitive and other behavioral deficits. The psychiatric disorders in patients with epilepsy are often missed and therapeutic opportunities are lost which can significantly impair the quality of life in them. Therefore, systematic identification of neuropsychiatric complications of anti-seizure medications must be done by the clinicians even in patients with adequately controlled seizures.

Future directions

More pragmatic quality of life assessment tools can be developed for use in outpatient clinics; to monitor the treatment outcomes including the neuropsychiatric adverse effect profile of anti-seizure medications.

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Conflicts of interest

There are no conflicts of interest.

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