Original Article

Depression and anxiety among patients with epilepsy: A cross-sectional study from Riyadh, Saudi Arabia

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Abstract

Background: It is well established that epileptic disorders are associated with a wide range of psychosocial issues that overburden the affected individuals and limit their lifestyle. This study aimed to determine the commonalities between depression and anxiety symptoms among patients with epilepsy (PWE). In addition, we assessed whether depression and anxiety rates varied depending on factors related to the disease. **Materials and Methods:** A cross-sectional study was conducted between October 2021 and March 2022 among all PWE at Prince Mohammed bin Abdulaziz Hospital, and 147 patients who responded to the questionnaires were included for analysis (65.6% response rate). Depression was measured using the Patient Health Questionnaire depression scale (PHQ-9), while anxiety levels were measured using the Generalized Anxiety Disorder scale (GAD-7). Demographic variables such as sex, age, marital status, and factors related to epilepsy were also recorded. **Results:** The results showed that 39.5% and 27.9% of participants had major depressive disorder (MDD) and generalized anxiety disorder (GAD), respectively. The presence of factors that increased susceptibility to seizures was associated with a greater expression of depression ($P = 0.035$) and anxiety ($P = 0.002$) symptoms. The presence of symptoms/signs that precede seizures was associated with a higher risk of moderate and severe depression ($P = 0.001$) and moderate and severe anxiety ($P < 0.001$). Irregular use of medications was associated with a higher risk of moderate and severe depression ($P = 0.037$); however, lamotrigine was associated with lower rates of depression among the participants ($P = 0.023$). **Conclusion:** This study found that PWE had a higher prevalence of MDD and GAD than the general population. However, this accepted paradigm has yet to reflect a meaningful change in constructing condition-specific recommendations for PWE. Our study revealed that the presence of subjectively recognized signs of an impending ictal episode was significantly associated with a higher risk of moderate and severe depression and anxiety. Furthermore, factors that increase the susceptibility to seizures were associated with a higher risk of depression and anxiety. Irregular medication use was associated with a higher risk of moderate and severe depression. However, lamotrigine was associated with lower rates of depression among participants.

Keywords: Anxiety, depression, epilepsy, prevalence

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Introduction

The association between epilepsy and psychiatric morbidities has long been recognized, and since the age of Hippocratic medicine, such observations have been made by noting the

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proclivity of patients with epilepsy (PWE) to be afflicted with melancholy.[1] This has been repeatedly proven across many populations, with the proposed introduction of a so-called interictal dysphoric disorder, which potentially allows uniform criteria for the diagnosis and management of such phenomena.[2] It is well established that epileptic disorders are associated with a wide range of psychosocial issues that overburden the affected individuals and limit their lifestyle, independence, and overall quality of life (QoL), such as academic underachievement and embarrassment associated with social stigma. In addition, PWE shows an increasing number of coexisting mental health disorders, particularly anxiety and depression, with incidence rates at least three-fold more than the general population,[3] and higher than those with other chronic medical conditions such as diabetes and asthma.[4]

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are the two most common psychiatric comorbidities in PWE.[5] Depression is considered the most commonly diagnosed psychiatric disorder in PWE, with a prevalence of 9.6–37.71%, while other studies have estimated the lifetime prevalence to be as high as 55%. More recent studies have suggested that anxiety, which has been described by many as a forgotten psychiatric comorbidity in PWE, may be more common than depressive disorders, with a prevalence between 19 and 42.6%.[6-12]

The relationship between depression, anxiety, and epilepsy is complex and remains underappreciated. Moreover, failure to recognize these comorbid psychiatric disorders is thought to be associated with reduced quality of life, increased seizure frequency, and higher rates of drug-refractory epilepsy and suicide.[13] Given that primary care physicians are often the first point of contact for patient care, it may therefore be requisite for primary care physicians to screen for coexisting mood disorders among PWE. The relationship can be described as multifactorial since psychiatric symptoms can emerge in PWE as a result of the original disease process, caused by seizures, antiepileptic medications, genetic predisposition, or social circumstances. Determining the offending factor is difficult and sometimes cannot be established because it requires extensive exploration and knowledge of multifactorial interactions.[14] Based on the growing concern, our study aimed to explore the association between specific antiepileptic medications and negative psychiatric symptoms in PWE. Previous studies have found that the prevalence of depressive symptoms was different in PWE using different medications and was higher with topiramate, barbiturates, and vigabatrin, this calls for an integrative approach in patient management spearheaded by primary care physicians, as the natural course of such conditions inexorably influences the quality of life of PWE.[15-17] Our study aimed to determine the prevalence of depression and anxiety symptoms among PWE who visited the neurology clinic at Prince Mohammed bin Abdulaziz Hospital (PMAH). The diagnoses of MDD and GAD are often guided by the clinical application of a set of criteria that can classify each disorder (e.g. DSM-5). MDD and GAD can be evaluated using the rapid screening tools, PHQ-9 and GAD-7, respectively. A score >10 defines the diagnosis of MDD, while a cutoff point of 10 applies to GAD using the respective validated screening instrument for each disorder.[18,19] In addition, depression and anxiety rates were assessed as functions of epilepsy duration, frequency of ictal episodes, and somatic distribution. Subjectively identified factors were assessed by screening for increased susceptibility to ictal episodes, the presence of preictal symptoms, and the number of medications used to control the conditions.

Materials and Methods

Study design and population

This cross-sectional study was conducted between October 2021 and March 2022 among PWE at Prince Mohammed bin Abdulaziz Hospital, a secondary center in Riyadh, Saudi Arabia. All patients diagnosed with epilepsy and followed up in neurology clinics (n = 224) were contacted over the phone, and the questionnaire was administered by trained researchers. This method ensured that the patients fully understood the questions and all data were collected. The study was explained to the participants, and informed consent was obtained. Participants were interviewed using a standardized questionnaire to measure depression and anxiety. A total of 147 patients completed the questionnaire, with a 65.6% response rate. This study was approved by the Institutional Review Board of the Central Second Health Cluster.

Survey instruments

The patients were contacted by phone and interviewed using a questionnaire consisting of three parts: [1] demographic variables such as gender, age, and marital status; factors related to the epilepsy such as (duration of epilepsy), (seizure free time), (seizure involvement), (medication use, compliance, and side effects), (presence of factors that increase the susceptibility to seizures), and (presence of symptoms/signs that precedes seizure attack); [2] the previously validated Arabic versions of the Patient Health Questionnaire depression scale (PHQ-9), and [3] the Generalized Anxiety Disorder scale (GAD-7). Patients >15 years and with a verified diagnosis of epilepsy in the hospital's electronic medical records were included in the study. Patients who were unable to answer the questionnaire due to communication or intellectual impediments were eliminated due to the difficulty in obtaining the information.

PHQ-9

The presence and severity of depression were evaluated using the Arabic version of the PHQ-9.[20] The PHQ-9 is a self-reported, nine-item questionnaire used to measure depression and its severity in the last two weeks. The responses were recorded as follows: not at all = 0; some days = 1; most days = 2; and every day = 3. The PHQ-9 responses were used to classify patients as having no (0–4), mild (5–9), moderate (10–14), moderate to severe (15–19), or severe depression (20–27). Patients with

moderate-to-severe and severe depression were grouped before analysis.

GAD-7

The Arabic version of the GAD-7 is a seven-item self-rating questionnaire.[20] Each item reflects a typical symptom of generalized anxiety disorder, and its significance is determined by how frequently it manifested during the previous two weeks. The responses were recorded as follows: not at all = 0; some days = 1; most days = 2; and every day = 3. The total GAD-7 score was used to classify patients as having no (0–4), mild (5–9), moderate (10–14), or severe anxiety (15–21).

Statistical analysis

Statistical analyses were performed using R v 3.5.3. Categorical variables are summarized as counts and percentages. Continuous normal and non-normal variables are represented by mean ± standard deviation or median/interquartile range [IQR], respectively. The Chi-square test of independence was used to assess the association between categorical variables, with goodness-of-fit variation of the same test to actualize a statistically significant comparison with previously published population estimates. Spearman's correlation was used to assess the associations between continuous variables.

Results

The study sample included 147 participants, comprised equally of men and women. The mean age was 32. Among them, 40.1% were married, while the remaining were single. Duration of the disease was less than 4 years in 25.2% of the participants and was more than 9 years in 46.9%. Seizures involved the whole body in 81% of the participants and affected a certain part of the body in 19%. Epilepsy was controlled in two-thirds of the participants in the past three months (63.9%). Regarding epilepsy medications, more than half reported using only one medication (66.7%) and less than one-third reported using two medications (28.6%). The majority of participants used the medications regularly (87.1) [Table 1].

Table 1: Descriptive statistics for the study sample

	[ALL]=*n*=147
Age	32.0 [24.0;43.0]
Gender:	
Female	73 (49.7%)
Male	74 (50.3%)
Marital status:	
Married	59 (40.1%)
Single	88 (59.9%)
Duration of epilepsy:	
<4 years	37 (25.2%)
4–8 years	41 (27.9%)
9+years	69 (46.9%)
Seizures involvement/distribution	
Certain body area	28 (19.0%)
Whole body	119 (81.0%)
Seizure controlled during the last 3 months:	
No	53 (36.1%)
Yes	94 (63.9%)
Epilepsy medications:	
1	98 (66.7%)
2	42 (28.6%)
3	7 (4.76%)
Regular use of medications:	
No	19 (12.9%)
Yes	128 (87.1%)

Table 2: A comparison between the proportion of GAD and MDD between PWE and the overall Saudi population

	This study (*n*=147)	Saudi National Mental Health Survey	*P*
Major depressive disorder (MDD)	39.5%	6%	<0.001
Generalized anxiety disorder (GAD)	28.6%	1.9%	<0.001

Prevalence of depression and anxiety

The results showed that 39.5% and 27.9% of participants had MDD and GAD, respectively. The prevalence of MDD and GAD in comparison with the most recent estimates from the Saudi National Mental Health Survey was statistically significant ($P < 0.001$) for both anxiety and depression [Table 2].

Univariate analysis of factors associated with depression and anxiety

The presence of factors that increased the susceptibility to seizures including sleep deprivation, stress, and anger was associated with higher levels of depression and anxiety ($P = 0.035$ and $P = 0.002$, respectively). The irregular use of medications was associated with a higher risk of moderate and severe depression ($P = 0.037$). The presence of symptoms/signs that precede seizures was associated with a higher risk of moderate and severe depression ($P = 0.001$) and a higher risk of moderate and severe anxiety ($P < 0.001$), the most commonly reported symptoms were uncontrolled eye movement and dizziness. None of the remaining factors was significantly associated with the risk of depression or anxiety [Tables 3 and 4].

Association between MDD and GAD with different medication use

[Table 5] shows the use of different medications according to the presence or absence of MDD and GAD. The use of different medications was not significantly different based on GAD or MDD, except for lamotrigine ($P = 0.023$), which was significantly higher in participants without MDD (22.5%) than in those with MDD (6.9%).

Discussion

The primary objective of our study was to estimate the prevalence of MDD and GAD among patients with epilepsy (PWE),

Table 3: Univariate analysis of factors associated with depression

	No depression *n*=58	Mild *n*=29	Moderate *n*=26	Severe *n*=34	*P*-overall
Age	32.5 [25.0–42.8]	34.0 [23.0–47.0]	32.5 [25.2–36.8]	30.0 [23.2–42.8]	0.811
Duration of epilepsy:					
<4 years	15 (25.9%)	3 (10.3%)	9 (34.6%)	10 (29.4%)	0.293
4–8 years	12 (20.7%)	10 (34.5%)	8 (30.8%)	11 (32.4%)	
9+years	31 (53.4%)	16 (55.2%)	9 (34.6%)	13 (38.2%)	
Seizures involvement/distribution:					
Certain body area	9 (15.5%)	4 (13.8%)	6 (23.1%)	3 (8.82%)	0.600
Whole body	49 (84.5%)	25 (86.2%)	20 (76.9%)	31 (91.18%)	
Seizure controlled during the last 3 months:					
Uncontrolled	19 (32.8%)	8 (27.6%)	14 (53.8%)	12 (35.3%)	0.191
Controlled	39 (67.2%)	21 (72.4%)	12 (46.2%)	22 (64.7%)	
Regular use of medications:					
No	7 (12.1%)	0 (0.00%)	5 (19.2%)	7 (20.6%)	0.037
Yes	51 (87.9%)	29 (100%)	21 (80.8%)	27 (79.4%)	
Presence of factors that increase the susceptibility to seizures					
No	31 (53.4%)	15 (51.7%)	11 (42.3%)	8 (23.5%)	0.035
Yes	27 (46.6%)	14 (48.3%)	15 (57.7%)	26 (76.5%)	
Presence of symptoms/signs that precedes seizure attack					
No	33 (56.9%)	17 (58.6%)	18 (69.2%)	7 (20.6%)	0.001
Yes	25 (43.1%)	12 (41.4%)	8 (30.8%)	27 (79.4%)	

Table 4: Univariate analysis of factors associated with anxiety

	No anxiety *n*=67	Mild *n*=38	Moderate *n*=22	Severe *n*=20	*P*
Age	34.0 [25.0–43.0]	32.5 [25.0–36.8]	30.0 [22.2–50.8]	29.5 [23.2–44.0]	0.595
Duration of epilepsy:					
<4 years	18 (26.9%)	10 (26.3%)	5 (22.7%)	4 (20.0%)	0.931
4–8 years	20 (29.9%)	7 (18.4%)	6 (27.3%)	8 (40.0%)	
9+years	29 (43.3%)	21 (55.2%)	11 (50%)	8 (40.0%)	
Seizures involvement/distribution:					
Certain body area	11 (16.4%)	6 (15.8%)	4 (18.2%)	1 (5.00%)	0.885
Whole body	56 (83.6%)	32 (84.2%)	18 (81.8%)	19 (95.0%)	
Seizure controlled during the last 3 months:					
Uncontrolled	21 (31.3%)	15 (39.5%)	9 (40.9%)	8 (40.0%)	0.754
Controlled	46 (68.7%)	23 (60.5%)	13 (59.1%)	12 (60.0%)	
Regular use of medications:					
No	7 (10.4%)	3 (7.89%)	5 (22.7%)	4 (20.0%)	0.254
Yes	60 (89.6%)	35 (92.1%)	17 (77.3%)	16 (80.0%)	
Presence of factors that increase the susceptibility to seizures					
No	39 (58.2%)	17 (44.7%)	4 (18.2%)	5 (25.0%)	0.002
Yes	28 (41.8%)	21 (55.3%)	18 (81.8%)	15 (75.0%)	
Presence of symptoms/signs that precede seizures					
No	47 (70.1%)	19 (50.0%)	5 (22.7%)	4 (20.0%)	<0.001
Yes	20 (29.9%)	19 (50.0%)	17 (77.3%)	16 (80.0%)	

using the PHQ-9 and GAD-7 as screening tools. In the present study, 39.5% of the participants had depression, which was in contrast to that reported previously (Mubaraki 2021) in a study conducted with the same screening tool in a different Saudi city, and showed 76.7% prevalence of depression among PWE. However, it is worth noting that our study utilized the more conventional 10 cutoff point to define the major depressive disorder, whereas the previous study included those with mild depression (PHQ-9, 5–10) as part of the total percentage.[21] The prevalence of GAD in our cohort was 27.9%, which, to our knowledge, marks the first estimate of GAD among PWE in Saudi Arabia, despite anxiety being the second most common psychiatric comorbidity. A meta-analysis of 23 articles published by The American Academy of Neurology found depression to be prevalent in nearly 20% of PWE cases, considering that the methods to diagnose depression were heterogeneous across the included studies.[22] Our results agree with those reported in the region and neighboring countries, with a prevalence ranging

Table 5: Association between epilepsy medications, anxiety, and major depressive disorders

	MDD			GAD		
	No *n*=89	Yes *n*=58	*P*	No *n*=106	Yes *n*=41	*P*
Carbamazepine:						
No	78 (87.6%)	52 (89.7%)	0.913	92 (86.8%)	38 (92.7%)	0.399
Yes	11 (12.4%)	6 (10.3%)		14 (13.2%)	3 (7.32%)	
Lamotrigine:						
No	69 (77.5%)	54 (93.1%)	0.023	86 (81.1%)	37 (90.2%)	0.275
Yes	20 (22.5%)	4 (6.90%)		20 (18.9%)	4 (9.76%)	
Levetiracetam:						
No	32 (36.0%)	17 (29.3%)	0.512	39 (36.8%)	10 (24.4%)	0.217
Yes	57 (64.0%)	41 (70.7%)		67 (63.2%)	31 (75.6%)	
Phenytoin:						
No	86 (96.6%)	55 (94.8%)	0.681	100 (94.3%)	41 (100%)	0.186
Yes	3 (3.37%)	3 (5.17%)		6 (5.66%)	0 (0.00%)	
Topiramate:						
No	86 (96.6%)	55 (94.8%)	0.681	103 (97.2%)	38 (92.7%)	0.349
Yes	3 (3.37%)	3 (5.17%)		3 (2.83%)	3 (7.32%)	
Valproic acid:						
No	66 (74.2%)	49 (84.5%)	0.201	82 (77.4%)	33 (80.5%)	0.850
Yes	23 (25.8%)	9 (15.5%)		24 (22.6%)	8 (19.5%)	
Stopped using medications currently:						
No	86 (96.6%)	54 (93.1%)	0.435	101 (95.3%)	39 (95.1%)	1.000
Yes	3 (3.37%)	4 (6.90%)		5 (4.72%)	2 (4.88%)	

from 22.8 to 31.3% and 26 to 48.5% for MDD and GAD, respectively.[23-26] The prevalence of MDD and GAD according to the latest Saudi National Mental Health Survey in 2017 was 6% and 1.9%, respectively;[27] we tested against these estimates with the assumption of unequal prevalence, and a statistically significant association was found. Therefore, we can reasonably infer the nonrandomness of our findings and that indeed, our cohort was more likely to have depression or anxiety than the general population. The reasons for such disparities are likely bidirectional and multifactorial, as evidence suggests a three- to seven-fold increased risk of epilepsy in patients with MDD.[28,29] In contrast, the natural course of epilepsy is likely to predict the occurrence of depression, and one study showed that people with frequent episodes (once or more per month) were five times more likely to be depressed than those who were seizure-free for the past year.[30]

Moreover, the presence of symptoms that heralded the onset of an ictal episode was significantly associated with GAD and MDD. However, further investigation is required to investigate whether these symptoms contribute to the etiology of psychiatric disorders, as auras become associated with feelings of inevitable impending doom. Therefore, prospective analyses targeting such symptoms for future psychotherapeutic interventions are required to terminate the evolution of this symptomatology into the full clinical expression of GAD or MDD. Subjectively identified factors preceding the onset of seizures were also significantly associated with a diagnosis of GAD and MDD, and 39% of our participants identified emotional factors (e.g., anger, stress, crying) as the preictal culprits of an ictal episode, further supporting the impact of psychological states on ictal conditions; this calls for vigilance in implementing screening methods for mood disorders. Taken together, these findings call for a more comprehensive individualized plan that is well tuned to the psychological profiles of PWE, as mood disorders seem to be inexorably linked with the natural course of epilepsy. Screening tools implemented by primary care physicians and clinical neurologists are likely to identify latent cases of depression and anxiety, which would theoretically reflect an improvement in the health-related quality of life. Additionally, subsyndromic complaints are equally significant in their influence on a medical condition, a new diagnostic entity introduced in DSM-5 is "psychological factors affecting other medical conditions" (PFAOMC), in which the natural course of a medical disorder is altered by psychological factors, these include sadness, regression, anxiety, denial, or anger.[31] Such complaints are best addressed by psychosomatic counseling rather than pharmacotherapy, thus it is pivotal for primary care physicians and neurologists alike to assume a holistic approach to treat the patient rather than a specific disorder. It is likely that our cohort included those who met the criteria for PFAOMC, as 39% identified emotional factors influencing their ictality. Cognitive behavioral therapy (CBT) has been found to be effective in improving the QoL of PWE, a valuable tool in the armamentarium of physicians caring for PWE.

We stratified our cohort in accordance with the pharmacological plan for controlling epilepsy, noting the well-known association between antiepileptic medications and depression. Lamotrigine was significantly associated with the absence of depressive status

in our cohort, which further corroborates previous studies indicating its usefulness as an option for PWE with comorbid MDD.[32-34]

This study has some limitations; namely, the smaller sample size and its monocentric nature precludes us from generalizing the results to the representative population. Furthermore, there is evidence of variations in the propensity for antiepileptic drugs to coexist with depression in a temporally suspicious manner. Combining qualitative methods may provide grounds for assessing the cultural background influences that address the seemingly increased occurrence of depression among PWE in Saudi Arabia.

Conclusion

This study found that patients with epilepsy have a higher prevalence of MDD and GAD than the general population. However, this accepted paradigm has yet to reflect a meaningful change in constructing condition-specific recommendations for PWE. Our study revealed that the presence of subjectively recognized signs of an impending ictal episode was significantly associated with a higher risk of moderate and severe depression and anxiety. Furthermore, factors that increase the susceptibility to seizures are associated with a higher risk of depression and anxiety. Irregular medication use was associated with a higher risk of moderate and severe depression. However, lamotrigine was associated with lower rates of depression among participants.

Acknowledgment

None

Abbreviation

PWE = Patients with epilepsy
MDD = Major depressive disorder
GAD = Generalized anxiety disorder
PHQ-9 = Patient health questionnaire-9
GAD-7 = Generalized anxiety disorder-7
QoL = Quality of life
PFAOMC = Psychological factors affecting other medical conditions

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Conflicts of interest

There are no conflicts of interest.

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