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Research Article

Evaluating the Psychiatric Sequelae of Long-Term Anti-Epileptic Medication Use in Adult Epilepsy Patients in Pakistan

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Abstract

Background: Long term anti epileptic drug (AED) therapy is required for epilepsy, a disorder of the nervous system, for which the sequelae might be associated with significant psychiatric problems. However, despite growing international awareness, there are few data from lower and lower-income countries such as Pakistan, where integrated neuropsychiatric screening is rarely practiced. The purpose of this study was to determine the prevalence and predictors of psychiatric morbidity in adult epilepsy patients on prolonged AED treatment.

Methods: The study was conducted cross-sectionally at Ghurki Trust Teaching Hospital, Lahore, and Farooq Hospital, Lahore, Pakistan from November 2023 to October 2024 . Forty-five adult patients (≥ 18 years) with a proven diagnosis of epilepsy and on AED therapy for 12 months or more were enrolled. Hospital Anxiety and Depression Scale (HADS) and Mini International Neuropsychiatric Interview (MINI) were used to assess psychiatric symptoms. Demographic, clinical, pharmacologic, and biochemical data (serum B12, folate, and calcium) were recorded and analyzed in SPSS version 27.0

Results: 60% of patients had depression (HADS ≥8) and 48% anxiety. Major depressive disorder was diagnosed in 26%, generalized anxiety disorder in 18%, and psychotic symptoms in 6% by MINI-based diagnoses. A significantly greater psychiatric morbidity was found in patients on polytherapy than in those on monotherapy ($p < 0.05$). More commonly, polytherapy users had nutritional deficiencies. There was a significant correlation between longer AED duration and higher depression scores ($p = 0.031$, $R^2 = 0.42$).

Conclusion: Adult epilepsy patients on long-term AEDs have a high prevalence of psychiatric morbidity, especially those on polytherapy and older agents. Improvement in neuropsychiatric outcomes in epilepsy care requires routine psychiatric screening and optimization of AED regimens.

Keywords: Epilepsy, Anti-epileptic drugs, Psychiatric comorbidity, Depression, Anxiety, Polytherapy, Long-term drug therapy, Pakistan, Neuropsychiatric effects, Seizure management

Introduction

Epilepsy is a chronic neurological condition that is characterized by recurrent seizures (unprovoked by an identifiable cause) and abnormal electrical activity in the brain. It is one of the most common neurological disorders around the world, affecting over 50 million people worldwide[1]. About 80 per cent of people with epilepsy live in low and middle-income countries (LMICs) where diagnosis and management are substandard due to resource limitations, social stigma, and lack of specialised care. Anti-epileptic drugs (AEDs) are long-term treatments and, in 70% of cases, allow epilepsy to be managed. On the other hand, AEDs are also known to have a wide range of psychiatric and behavioral side effects, most notably of which are side effects of long-term use[2].

Epilepsy is a major disease in Pakistan, with a prevalence rate estimated to range from 9.9 to 14.8 per 1,000 population, which is much higher than what is commonly reported in other developed countries. Epilepsy makes up about 10 per cent of neurological outpatient consultations, say regional hospital data[3]. Lack of access to other therapies, such as surgery or neuromodulation, means most patients require lifelong pharmacological treatment. Epilepsy is a chronic condition, and cultural stigmatization and limited availability of mental health services make this a vulnerable environment for psychiatric comorbidities to develop. Studies in other similar LMIC settings have demonstrated that between 20% and 60% of epilepsy patients experience some form of psychiatric disorder during their treatment course but fail to be diagnosed and treated[4, 5].

Long-term AED use has been associated with psychiatric sequelae, including depression, anxiety, irritability, apathy, mood swings, and suicidal ideation, which can progress to psychosis. Several factors influence these adverse effects, including the type of AED, duration of therapy, polytherapy status, individual susceptibility, and a pre-existing vulnerability to psychiatric illness[6]. Commonly used in Pakistan, but also quite old generation AEDs, such as phenobarbital and carbamazepine, have been associated with higher rates of mood disturbances and cognitive impairments. Some newer AEDs, such as levetiracetam and topiramate, even some of the newest AEDs, can make anxiety or depressive symptoms worse, especially in predisposed people[7].

In epilepsy management, attention has been given worldwide to mental health concerns, which now includes the clinical guideline to include routine psychiatric screening with seizure control. But in Pakistan, this integration has not taken place[8]. Low mental health literacy, inadequate supply of psychiatric workforce (estimated to be fewer than 500 psychiatrists among over 240 million people), and limited access to psychological services contribute to underreporting and underdiagnosis of these critically important psychiatric outcomes. Therefore, many patients live with seizures but have a good quality of life, and they are seizure-free[9].

Consideration of this aspect of care in the Pakistani healthcare system is necessary, given the psychosocial, clinical, and economic implications of untreated psychiatric comorbidities in epilepsy. The purpose of this study is to assess the prevalence and nature of the psychiatric sequelae of long-term AED use in adult epilepsy patients in Pakistan. The study aims to shed light on this often-overlooked aspect with a view to contributing evidence to integrated, multidisciplinary epilepsy management strategies that may be developed for the Pakistani population[10].

Materials and Methods

Study Design and Setting

A cross-sectional observational study spanning 12 months (November 2023 to October 2024) was conducted in two tertiary care teaching hospitals of Lahore , Ghurki Trust Teaching Hospital, and Farooq Hospital, Lahore, Pakistan.

Study Population

Adult patients (age 18 years or older) with a confirmed clinical diagnosis of epilepsy were enrolled from the Neurology Outpatient Department. Patients, to be eligible, had to have been on continuous anti-epileptic drug (AED) therapy for at least 12 months. Patients were enrolled by a consecutive nonprobability sampling technique during their scheduled follow-up visits.

Inclusion and Exclusion Criteria

Patients with a documented diagnosis of epilepsy with at least one year of uninterrupted AED use and able to give informed written consent were included in the study and met the inclusion criteria. Patients were excluded if they had a previous history of psychiatric illness before AED initiation, ongoing substance abuse, severe cognitive impairment, or poor compliance with AED therapy. Exclusion was also made for cases with incomplete clinical or biochemical records.

Sample Size Justification

As feasibility, expected outpatient volume and alignment with previous psychiatric-evaluation studies in resource-constrained settings allowed, 50 total patients were included. This sample size provides the opportunity for meaningful statistical interpretation of psychiatric outcomes and subgroup comparisons without exceeding the study resources.

Ethical Considerations

The Institutional Review Board approved the Ethical approval for the current study. The study objectives, procedures, and the patients' rights (voluntary participation and the right to withdraw at any stage) were briefed to all patients. Strict confidentiality was maintained, and written informed consent was secured.

Data Collection Tools and Procedure

Demographic variables (age, gender, education, occupation, residence), clinical details (type of epilepsy, duration of illness, seizure frequency), AED regimen (monotherapy vs. polytherapy), and treatment duration were collected using a structured data collection form. Serum levels of vitamin B12, folate, and calcium in the laboratory records were reviewed and analyzed as potential biochemical contributors to psychiatric outcomes.

Two validated instruments were used to conduct the psychiatric evaluation. To quantify anxiety and depressive symptoms, we used the Hospital Anxiety and Depression Scale (HADS), and a score of ≥8 on each subscale was considered indicative of clinically significant symptoms. The Mini International Neuropsychiatric Interview was completed for diagnostic confirmation of major depressive disorder, generalized anxiety disorder, psychosis, and suicidality using DSM-5 criteria. Medical officers trained in conducting interviews in Urdu or English conducted interviews in Urdu or English as preferred by the participant, under the supervision of consultant psychiatrists.

Statistical Analysis

IBM SPSS Statistics Version 27.0 was used to enter and analyse the data. Participant characteristics were summarized using descriptive statistics, including means, standard deviations, frequencies, and percentages. Inferential analysis consisted of chi-square tests and Fisher's exact tests for categorical variables and independent t-tests for continuous variables. The association between AED duration and depression score was measured using a linear regression model. Statistically significant was considered at a <0.05 p-value.

Results

A total of n=50 adult patients with epilepsy under long term anti epileptic drug (AED) therapy were included in the study. The age of participants was 34.2 ± 11.5 years, between 18 and 60 years. The ratio of males to females was 1.27:1, 28 (56%) males and 22 (44%) females, leading to a male predominance. Body mass index (BMI) averaged 23.6 ± 3.9 kg/m^2, and 14% were underweight, 62% were within the normal range, and 24% were overweight. Most (70%) of the patients resided in urban areas, while 30% were from rural communities.

They were found to have an educational background where 6 (12%) were illiterate, while 18 (36%) had completed secondary education, 14 (28%) had intermediate level education, and 12 (24%) had graduate or more. The occupational status was 16 (32%) unemployed, 9 (18%) students, 17 (34%) engaged in informal jobs, and 8 (16%) in the formal sector of employment. Table 1 presents these socio-demographic variables as shown in table1.

Table 1: Socio-demographic and Baseline Clinical Characteristics of Epilepsy Patients (n = 50)

Variable	Category	n	%
Age (years)	Mean ± SD	–	34.2 ± 11.5
Gender	Male	28	56.0
	Female	22	44.0
Body Mass Index (kg/m^2)	Underweight (<18.5)	7	14.0
	Normal (18.5–24.9)	31	62.0
	Overweight (≥25)	12	24.0
Residence	Urban	35	70.0
	Rural	15	30.0
Educational Level	Illiterate	6	12.0
	Secondary education	18	36.0
	Intermediate (FA/FSc)	14	28.0
	Graduate or higher	12	24.0
Occupation	Unemployed	16	32.0
	Student	9	18.0
	Informal employment	17	34.0
	Formal employment	8	16.0

Thirty-six (72%) patients had generalized epilepsy, and fourteen (28%) had focal epilepsy clinically. Epilepsy had lasted for a mean of 6.8 ± 3.2 years, and the mean seizure frequency was 2.4 ± 1.7 episodes per month. In the treatment, 27 (54%) patients were on monotherapy and 23 (46%) were on polytherapy. Amongst others, valproate (40%), carbamazepine (26%), levetiracetam (20%), and phenytoin (14%) were the most frequently used AEDs.

9 (18%) patients had biochemical deficiency of vitamin B12, 7 (14%) had low serum folate, and 6 (12%) had hypocalcemia (<8.5 mg/dL). Most of these deficiencies were seen in polytherapy users. Table 2 summarizes the complete clinical and AED profiles as shown in table 2.

Table 2: Clinical Characteristics and AED Profiles of Epilepsy Patients (n = 50)

Variable	Category	n	%
Type of Epilepsy	Generalized	36	72.0
	Focal	14	28.0
Duration of Epilepsy (years)	Mean ± SD	–	6.8 ± 3.2
Monthly Seizure Frequency	Mean ± SD	–	2.4 ± 1.7
AED Regimen	Monotherapy	27	54.0
	Polytherapy	23	46.0
Most Common AEDs Used	Valproate	20	40.0
	Carbamazepine	13	26.0
	Levetiracetam	10	20.0

	Phenytoin	7	14.0
Older-generation AEDs Only	Yes	11	22.0
	No	39	78.0
Vitamin B12 Deficiency	Present	9	18.0
	Absent	41	82.0
Low Serum Folate	Present	7	14.0
	Absent	43	86.0
Hypocalcemia (<8.5 mg/dL)	Present	6	12.0
	Absent	44	88.0

According to HADS scores, 30 (60%) of patients had depressive symptoms, and 24 (48%) had anxiety. In clinical interviews on the structured MINI diagnostic interview, 13 (26%) were found to have major depressive disorder, 9 (18%) had generalized anxiety disorder, and 3 (6%) had psychotic symptoms like hallucinations or delusions. 2 (4%) patients reported suicidal ideation.

Results of statistical analysis showed that psychiatric morbidity was significantly higher in those receiving polytherapy. This included more depression in polytherapy users (78.3%) than in monotherapy (44.4%, p = 0.012). For anxiety (60.9% vs. 37.0%, p = 0.037), major depression (34.8% vs. 18.5%, p = 0.041), and psychotic symptoms (13.0% vs. 0%, p = 0.022), similar trends were noted. Table 3 presents full psychiatric stratification by AED regimen as shown in table 3.

Table 3: Psychiatric Sequelae Stratified by AED Therapy Type

Psychiatric Outcome	Monotherapy (n = 27)	Polytherapy (n = 23)	p-value
HADS Depression (Score ≥8)	12 (44.4%)	18 (78.3%)	0.012 *
HADS Anxiety (Score ≥8)	10 (37.0%)	14 (60.9%)	0.037 *
Major Depressive Disorder (MINI)	5 (18.5%)	8 (34.8%)	0.041 *
Generalized Anxiety Disorder (MINI)	3 (11.1%)	6 (26.1%)	0.028 *
Psychotic Symptoms	0 (0%)	3 (13.0%)	0.022 *
Suicidal Ideation	0 (0%)	2 (8.7%)	0.033 *

*Statistically significant (p < 0.05)

Figure 1 is an additional visualization of these findings, depicting the comparative burden of psychiatric symptoms in monotherapy and polytherapy AED regimens, and psychiatric morbidity was highly variable between patients who received monotherapy versus those on polytherapy. As shown in Figure 1, depressive symptoms were seen in 78.3% of polytherapy users versus 44.4% of monotherapy users. Polytherapy patients were also more anxious (60.9% vs. 37.0%). Patients in the polytherapy group had significantly more diagnoses of major depressive disorder (34.8% vs. 18.5%) and generalized anxiety disorder (26.1% vs. 11.1%). In particular, psychotic features were observed in 13.0% of polytherapy patients and were not reported in the monotherapy group.

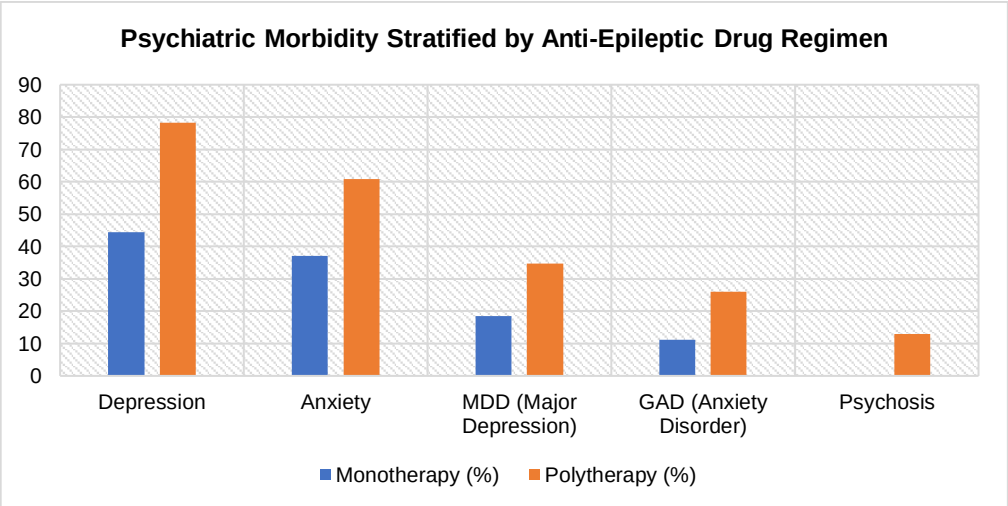

Figure 1: Psychiatric morbidity stratified by anti-epileptic drug regimen: *Patients receiving polytherapy exhibited significantly higher rates of depression, anxiety, major depressive disorder (MDD), generalized anxiety disorder (GAD), and psychotic symptoms compared to those on monotherapy ($p < 0.05$ for all).*

Figure 2: Scatter plot analysis of duration of AED use vs. HADS depression scores; linear correlation demonstrated. Those patients who had AED therapy for more than five years and had more than five years of continuous AED therapy were more likely to report moderate-to-severe depressive symptoms. This provides a dose duration effect, whereby longer AED exposure renders one more vulnerable to depressive outcomes. This observation was supported by linear regression analysis, which was statistically significant ($p = 0.031$, $R^2 = 0.42$).

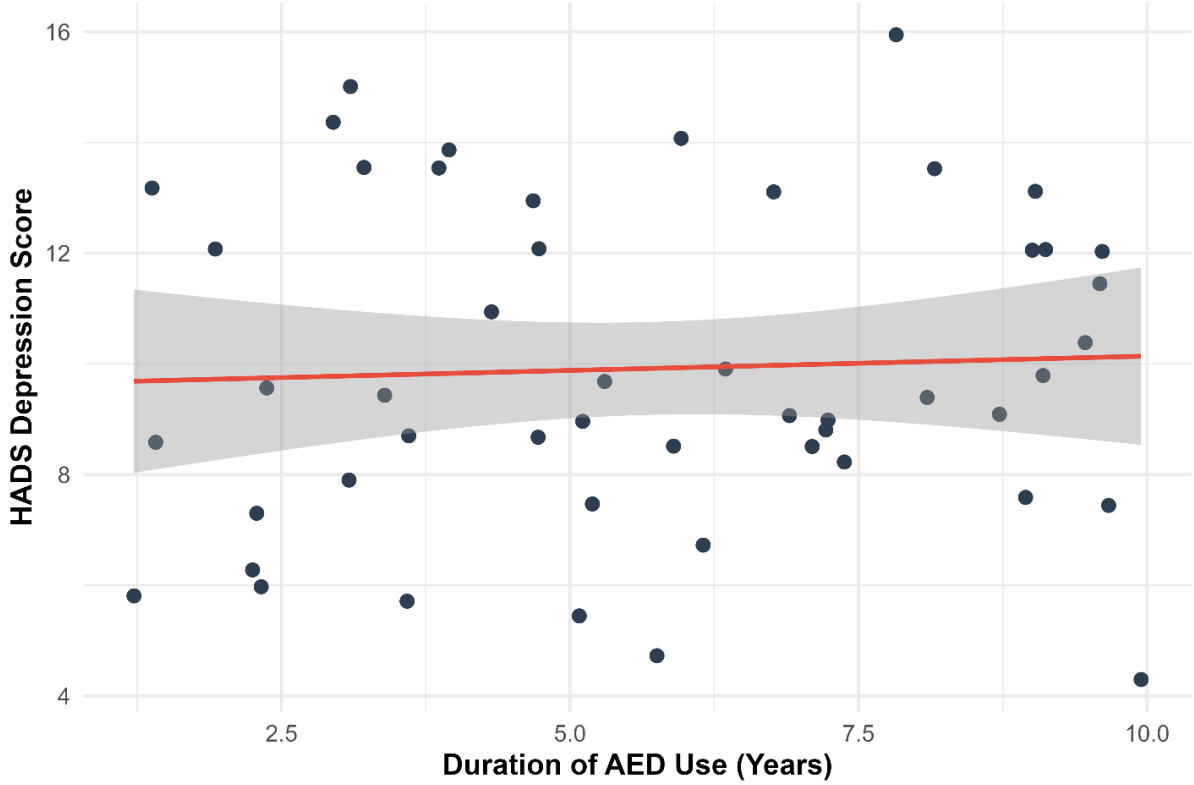

Figure 2: Correlation Between Duration of AED Use and HADS Depression Score: *Scatter plot showing a positive correlation between duration of anti-epileptic drug (AED) use and HADS depression scores. Prolonged therapy (>5 years) was associated with significantly higher depressive symptom severity ($p = 0.031$, linear regression, $R^2 = 0.42$).*

Taken together, these findings suggest a substantial burden of psychiatric morbidity in adult epilepsy patients on long term anti epileptic drug therapy, and a higher prevalence in those on polytherapy and prolonged treatment duration. Results indicate that integrated neuropsychiatric evaluation would be beneficial for epilepsy management in resource-limited clinical settings.

Discussion

This study aimed to determine the psychiatric sequelae of long term anti epileptic drug (AED) use in adult epilepsy patients in Pakistan. The prevalence of psychiatric morbidity is high, and we find that patients receiving polytherapy and those who have been on treatment for longer periods are at particular risk[11]. They were not only common but also significantly related to polypharmacy and exposure to older generation AEDs. This is consistent with the literature from the global community, which indicates that AEDs are neuroprotective and seizure suppressive, but they can induce or unmask psychiatric symptoms through their effects on neurotransmitter regulation, folate metabolism, and structural brain plasticity[12].

These effects have been explained by several mechanisms. Phenytoin and valproate have been shown to affect serotonergic and GABAergic activity, and carbamazepine has been linked to mood and cognition dysregulation due to modulation of sodium channels[13]. In addition, the AED-associated deficiencies in vitamin B12, folate, and calcium (as

seen in our cohort) may worsen neuropsychiatric instability and contribute to worsened symptoms of mood disorders. In addition, our finding of higher psychiatric symptom scores in patients with prolonged AED exposure is in the context of reports that chronic AED use is linked to cumulative metabolic derangements and declining psychosocial resilience[14].

Our data highlight a concerning underdiagnosis of psychiatric comorbidities in epilepsy care and countries like Pakistan, especially in low and middle-income countries. However, psychiatric disorders are very common in our study population, but they are not routinely screened in epilepsy management in most tertiary centers [15]. This is concerning because untreated depression and anxiety have been shown to increase seizure frequency, reduce quality of life, impair treatment adherence, and increase suicide risk. Finally, the presence of psychotic features in 6% of patients and suicidal ideation in 4% of the cohort further emphasizes the need for clinical attention to this problem[16, 17].

Importantly, the psychiatric burden observed was much more pronounced in the polytherapy patients. Polytherapy may be clinically required for seizure control in refractory patients, but it is associated with adverse psychiatric outcomes, and the risk-benefit ratio must be carefully balanced. Clinicians should as much as possible rationalize AED use, monitor psychiatric symptoms proactively, and consider early mental health referrals when possible. Furthermore, newer generation AEDs such as levetiracetam and lamotrigine are used if available to mitigate these risks, as they have relatively better neuropsychiatric tolerability profiles[18, 19].

Contribution from this study is important evidence from Pakistan, a country where epilepsy care is hindered by a lack of specialist access, high stigma, and fragmented mental health systems. Nevertheless, there remain some limitations[20]. By design, the cross-sectional approach prevents causal inference from AED use to psychiatric outcomes. Second, the sample size is pragmatic, but not generalizable. Third, we did not track psychiatric symptoms longitudinally or with AED dosage changes. Further elucidation of the pathophysiological pathways through which AEDs may impact psychiatric outcomes requires multicenter, prospective studies with neuroimaging and biomarker correlates [21].

However, our findings underscore a neglected aspect of epilepsy care in resource-limited settings. Routine psychiatric screening, nutritional monitoring, and interdisciplinary collaboration concerning epilepsy protocols are feasible as well as necessary to implement comprehensive patient-centered care[22, 23].

Conclusion

A substantial burden of psychiatric morbidity is associated with long-term use of anti epileptic drugs, particularly in the older generation medications in the setting of polytherapy in adult epilepsy patients. Highly prevalent depression, anxiety, and psychotic symptoms were seen in those on long treatment duration and biochemical deficiency. These results suggest the importance of incorporating mental health assessment into standard epilepsy care, increasing the number of AEDs administered, and implementing interprofessional management strategies to enhance seizure control and psychosocial outcomes in an at-risk group.

Conflict of Interest:
The authors declare that no conflicts of interest exist.
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Authors contribution:
All authors contributed equally to the current study.

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