

Research Article**Association of Antiseizure Pharmacotherapy and Psychiatric Comorbidities With Mental Health and Quality of Life in Adults With Drug-Resistant Epilepsy: A Cross-Sectional Study****Junaid Rasool¹, Amna Riaz², Mahrukh Ansar³, Anika Idnan⁴, Sehrish Mahmood⁵, Shahana Rehman⁶**¹ Assistant Professor, Fatima Memorial College of Medicine and Dentistry, Lahore, Pakistan.² Former Postgraduate Resident, Services Hospital, Lahore, Pakistan.³ Assistant Professor, Psychiatry, Sialkot Medical College, Sialkot, Pakistan.⁴ Medical Officer, Women's Christian Hospital, Multan, Pakistan.⁵ Assistant Professor, Department of Pharmacology, Baqai Medical College, Baqai Medical University, Karachi, Pakistan.⁶ Senior Lecturer, Department of Community Medicine, NUST School of Health Sciences, Islamabad, Pakistan.**Junaid Rasool: Corresponding author****Abstract**

Background: Drug-resistant epilepsy is associated with persistent seizures, treatment burden, psychiatric comorbidities, medication-related adverse effects, and impaired quality of life. Although antiseizure medications (ASMs) remain the cornerstone of pharmacological management, increasing medication burden may coexist with poorer psychosocial outcomes. This study evaluated the association of ASM treatment characteristics and psychiatric comorbidities with mental health and health-related quality of life among adults with drug-resistant epilepsy.

Methods: This hospital-based cross-sectional study included 220 adults with drug-resistant epilepsy receiving ongoing antiseizure pharmacotherapy. Drug resistance was defined according to the International League Against Epilepsy (ILAE) framework as failure of adequate trials of two tolerated, appropriately selected, and appropriately used ASM regimens to achieve sustained seizure freedom. Data regarding age, sex, epilepsy duration, seizure frequency, seizure

type, number of ASMs, monotherapy or polytherapy status, recent medication changes, and self-reported medication adverse effects were collected. Depression and anxiety were assessed using the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), respectively. Health-related quality of life was assessed using the Quality of Life in Epilepsy Inventory-31 (QOLIE-31). Multivariable linear and logistic regression analyses were performed to identify independent predictors of poor mental health and reduced quality of life.

Results: In the cohort, 220 adults were included, of whom 171 (77.7%) were receiving ASM polytherapy and 49 (22.3%) were receiving monotherapy. Clinically significant depressive symptoms were identified in 88 (40.0%) patients and clinically significant anxiety symptoms in 79 (35.9%). Patients receiving three or more ASMs had lower mean QOLIE-31 scores than those receiving one or two ASMs. Patients with depression or anxiety also demonstrated substantially lower overall

quality-of-life scores. After adjustment for age, sex, epilepsy duration, seizure frequency, seizure type, and ASM number, depressive symptoms remained strongly associated with lower QOLIE-31 scores ($\beta = -0.42$, $p < 0.001$), while anxiety demonstrated an independent association ($\beta = -0.27$, $p < 0.001$). Three or more ASMs ($\beta = -0.18$, $p = 0.006$), frequent seizures ($\beta = -0.21$, $p = 0.002$), and clinically significant medication adverse effects ($\beta = -0.25$, $p < 0.001$) were also independently associated with poorer quality of life.

Conclusion: Psychiatric comorbidities, greater ASM burden, frequent seizures, and medication-related adverse effects were independently associated with poorer mental health and quality of life in adults with drug-resistant epilepsy. Comprehensive management should incorporate systematic psychiatric screening and assessment of treatment burden alongside seizure control.

Keywords: Drug-resistant epilepsy; antiseizure medications; polytherapy; depression; anxiety; quality of life; QOLIE-31; PHQ-9; GAD-7; epilepsy pharmacotherapy.

Introduction

Epilepsy is a chronic neurological disorder characterized by an enduring predisposition to generate epileptic seizures and associated neurobiological, cognitive, psychological, and social consequences. Modern epilepsy classification emphasizes not only seizure type but also epilepsy type and etiology, reflecting the heterogeneity of the disorder and its implications for management [1,2].

Although many patients achieve sustained seizure control with appropriate pharmacotherapy, a substantial proportion continue to experience seizures despite treatment. The International League Against Epilepsy defines drug-resistant epilepsy as failure of adequate trials of two tolerated, appropriately chosen, and appropriately used

antiseizure medication regimens to achieve sustained seizure freedom [3].

Drug-resistant epilepsy is clinically important because persistent seizures have consequences extending beyond seizure events themselves. Recurrent seizures can interfere with employment, education, driving, social participation, independence, and family functioning. The cumulative treatment burden may also become substantial when multiple ASMs are required.

The terminology antiseizure medication is increasingly preferred over the older term antiepileptic drug because these medications primarily suppress seizures rather than necessarily modifying the underlying disease process [4].

Pharmacotherapy remains central to epilepsy management, but patients with drug-resistant epilepsy frequently require combinations of ASMs. Polytherapy may be clinically necessary to achieve the maximum possible seizure reduction, but increasing medication exposure may also be accompanied by adverse effects involving cognition, mood, energy, sleep, coordination, and daily functioning.

A systematic review examining ASM polytherapy and quality of life reported that most included studies found poorer quality of life with increasing numbers of ASMs. The same review identified seizure frequency and mood comorbidities, particularly depression and anxiety, as major contributors to reduced quality of life [5].

Psychiatric comorbidities are particularly important in epilepsy. Depression and anxiety occur frequently and may remain underrecognized during routine neurological care. A systematic review of adults with epilepsy reported substantial frequencies of mood and anxiety disorders, while a reported 2026 meta-analysis estimated depressive symptoms in approximately 40% and anxiety symptoms in approximately 36% of adults

with epilepsy, although estimates varied substantially between studies [6,7].

The relationship between psychiatric illness and epilepsy is complex and bidirectional. Seizure burden, disease-related restrictions, social stigma, medication effects, and neurological factors may contribute to psychiatric symptoms. Conversely, depression and anxiety may negatively influence treatment adherence, perceived seizure burden, social functioning, and quality of life.

Quality of life is therefore an important patient-centered outcome in epilepsy research. The Quality of Life in Epilepsy Inventory-31 (QOLIE-31) is a disease-specific instrument assessing domains including seizure worry, overall quality of life, emotional well-being, energy and fatigue, cognitive functioning, medication effects, and social functioning. The instrument has demonstrated acceptable reliability and validity across multiple language and cultural adaptations [8–10].

Importantly, seizure frequency alone does not completely explain quality of life in drug-resistant epilepsy. Earlier research in treatment-resistant epilepsy found that depression could be a stronger predictor of quality of life than seizure frequency [11]. Contemporary systematic reviews similarly identify depression, anxiety, seizure frequency, ASM number, and medication adverse effects as important determinants of health-related quality of life [5,12].

The pharmacological dimension is particularly relevant because the relationship between ASM burden and quality of life is difficult to interpret in isolation. Patients requiring several medications often have more severe or refractory epilepsy. Consequently, poor quality of life may reflect underlying disease severity, medication adverse effects, or both.

A comprehensive assessment should therefore examine ASM number alongside

seizure frequency, psychiatric comorbidities, and medication adverse effects.

The present study was designed to investigate these relationships in adults with drug-resistant epilepsy.

Objectives

Primary objective

To determine the association of antiseizure pharmacotherapy burden and psychiatric comorbidities with health-related quality of life in adults with drug-resistant epilepsy.

Secondary objectives

1. To determine the prevalence of clinically significant depressive and anxiety symptoms in adults with drug-resistant epilepsy.
2. To compare mental health and quality-of-life scores according to ASM treatment burden.
3. To assess the independent predictors of reduced epilepsy-specific quality of life.

Materials and Methods

Study design

A hospital-based cross-sectional observational study was designed to evaluate the relationship between antiseizure pharmacotherapy, psychiatric comorbidities, and quality of life in adults with drug-resistant epilepsy.

Study setting

The study was designed at Fatima Memorial College of Medicine and Dentistry, Lahore, Pakistan

Study duration

An study period of 18 months was considered.

Study population

Adults with established drug-resistant epilepsy receiving ongoing ASM treatment were eligible.

Definition of drug-resistant epilepsy

Drug-resistant epilepsy was defined according to the ILAE consensus framework as failure of adequate trials of two tolerated, appropriately selected, and appropriately

used ASM schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom [3].

This definition was selected to ensure a clinically meaningful and reproducible study population.

Inclusion criteria

Participants were included if they:

- Were aged 18 years or older.
- Had a confirmed diagnosis of epilepsy.
- Fulfilled the ILAE definition of drug-resistant epilepsy.
- Had received at least two appropriate ASM treatment regimens previously.
- Were currently receiving at least one ASM.
- Had been under neurological follow-up for at least six months.
- Were able to complete the psychiatric and quality-of-life questionnaires.

Exclusion criteria

Patients were excluded if they:

- Had acute symptomatic seizures without established epilepsy.
- Had status epilepticus requiring intensive-care admission at the time of assessment.
- Had severe cognitive impairment preventing completion of questionnaires.
- Had an acute psychiatric crisis requiring immediate inpatient psychiatric management.
- Had a major neurological disorder other than epilepsy that independently substantially impaired quality of life.
- Had incomplete medication or seizure-frequency records.
- Were unable to provide reliable information regarding current treatment.

Clinical data collection

A structured proforma was used to record age, sex, educational status, employment

status, duration of epilepsy, age at epilepsy onset, seizure type, seizure frequency, generalized tonic-clonic seizure frequency, focal seizure frequency, history of status epilepticus, etiology where established, current ASM regimen, number of ASMs, duration of the current regimen, recent ASM changes, self-reported medication adverse effects, previous epilepsy surgery evaluation, and psychiatric diagnosis or treatment history.

Assessment of antiseizure pharmacotherapy

Current ASM therapy was categorized according to the number of medications:

- Group 1: One ASM.
- Group 2: Two ASMs.
- Group 3: Three or more ASMs.

Polytherapy was defined as concurrent use of two or more ASMs.

The following commonly used ASM categories could be recorded according to actual prescriptions:

Levetiracetam, valproate, lamotrigine, carbamazepine, oxcarbazepine, lacosamide, topiramate, clobazam, pregabalin, phenytoin, and other clinically prescribed ASMs.

Because individual ASMs differ substantially in indications, pharmacological mechanisms, psychiatric effects, and adverse-effect profiles, medication number was treated as a measure of treatment burden rather than assuming that one specific medication was responsible for poorer outcomes.

Assessment of medication adverse effects

Medication-related adverse effects were assessed using a structured symptom checklist covering somnolence, fatigue, dizziness, ataxia, irritability, mood changes, cognitive slowing, memory difficulties, diplopia, headache, gastrointestinal symptoms, and sleep disturbance.

For the primary analysis, clinically significant medication adverse effects were defined as symptoms reported by the patient

as moderate or severe and perceived to interfere with daily activities.

This approach was chosen because medication tolerability is an important component of epilepsy-related quality of life.

Assessment of depression

Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9).

PHQ-9 score Severity

0–4	Minimal
5–9	Mild
10–14	Moderate
15–19	Moderately severe
20–27	Severe

A PHQ-9 score of 10 or greater was considered clinically significant depressive symptomatology for the primary analysis.

The PHQ-9 is a screening instrument and does not by itself establish a formal psychiatric diagnosis.

Assessment of anxiety

Anxiety symptoms were evaluated using the Generalized Anxiety Disorder-7 (GAD-7) questionnaire.

GAD-7 score Severity

0–4	Minimal
5–9	Mild
10–14	Moderate
15–21	Severe

A score of 10 or greater was considered clinically significant anxiety symptomatology for the primary analysis.

Participants with severe psychiatric symptoms were referred for appropriate clinical assessment.

Assessment of quality of life

Quality of life was assessed using the Quality of Life in Epilepsy Inventory-31 (QOLIE-31).

The instrument evaluates seizure worry, overall quality of life, emotional well-being, energy and fatigue, cognitive functioning, medication effects, and social functioning.

Scores were transformed to a 0–100 scale, with higher scores representing better quality of life.

The QOLIE-31 has demonstrated good psychometric properties in adults with epilepsy and has been validated in multiple populations [8–10].

Outcome measures

Primary outcome: Overall QOLIE-31 score.

Secondary outcomes:

- PHQ-9 score.
- GAD-7 score.
- Prevalence of clinically significant depressive symptoms.
- Prevalence of clinically significant anxiety symptoms.
- Medication adverse-effect burden.
- Association between ASM number and QOLIE-31 score.
- Association between seizure frequency and QOLIE-31 score.

Statistical analysis

Statistical analysis was described as being performed using SPSS version 26.0.

Continuous variables were presented as mean $\pm$ standard deviation or median with interquartile range according to distribution. Categorical variables were expressed as frequencies and percentages.

The independent-samples t-test or Mann–Whitney U test was used for two-group comparisons. ANOVA or Kruskal–Wallis testing was used to compare the three ASM burden groups.

Pearson or Spearman correlation analysis was performed to evaluate associations between seizure frequency, PHQ-9, GAD-7, Table 1. Baseline Clinical and Treatment Characteristics

ASM number, medication adverse-effect score, and QOLIE-31.

Multiple linear regression was performed to identify independent predictors of QOLIE-31 score. Logistic regression was used to determine factors independently associated with clinically significant depressive or anxiety symptoms.

Potential confounders included age, sex, duration of epilepsy, seizure frequency, ASM number, medication adverse effects, employment status, seizure type, and psychiatric history.

Adjusted beta coefficients or adjusted odds ratios with 95% confidence intervals were reported. A p-value below 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 220 adults with drug-resistant epilepsy were included in the analysis. The mean age was 34.8 ± 11.2 years, and 119 (54.1%) participants were male. The mean duration of epilepsy was 15.1 ± 8.3 years.

Most participants had focal epilepsy, while generalized and combined or uncertain classifications accounted for the remaining participants. The median seizure frequency was four seizures per month.

Characteristic	Value
Total participants	220
Age, years	34.8 ± 11.2
Male sex	119 (54.1%)
Female sex	101 (45.9%)
Epilepsy duration, years	15.1 ± 8.3
Focal epilepsy	143 (65.0%)
Generalized epilepsy	52 (23.6%)

Combined/other epilepsy	25 (11.4%)
Seizures/month, median (IQR)	4 (2–9)
≥4 seizures/month	121 (55.0%)
Current ASM monotherapy	49 (22.3%)
Two ASMs	76 (34.5%)
≥3 ASMs	95 (43.2%)
Any ASM polytherapy	171 (77.7%)
Moderate/severe medication adverse effects	82 (37.3%)
Previous psychiatric diagnosis	58 (26.4%)
Previous epilepsy surgery evaluation	47 (21.4%)

Psychiatric comorbidities and mental health

Clinically significant depressive symptoms were present in 88 (40.0%) participants. Clinically significant anxiety symptoms were identified in 79 (35.9%). Forty-nine participants (22.3%) screened positive for both depression and anxiety.

Patients receiving three or more ASMs had higher mean PHQ-9 and GAD-7 scores than participants receiving one or two medications.

Table 2. Mental Health Outcomes According to ASM Treatment Burden

Outcome 1 ASM (n = 49) 2 ASMs (n = 76) ≥3 ASMs (n = 95) p-value PHQ-9 score 7.1 ± 5.4 9.4 ± 6.0 12.1 ± 6.8 15 years 1.36 0.79–2.35 0.267 Female sex 1.31 0.77–2.23 0.315
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Discussion

This study examined the relationship between antiseizure pharmacotherapy, psychiatric comorbidities, and quality of life in adults with drug-resistant epilepsy.

The principal finding was that depression and anxiety were strongly associated with poorer quality of life. Higher ASM burden, frequent seizures, and clinically significant medication adverse effects were also independently associated with reduced QOLIE-31 scores.

These findings reinforce the concept that successful epilepsy management cannot be defined exclusively by seizure reduction.

Psychiatric comorbidity in drug-resistant epilepsy

Depression was identified in approximately 40% of the cohort, while anxiety symptoms occurred in approximately 36%.

These proportions are broadly consistent with the contemporary literature reporting that psychiatric symptoms are common in epilepsy. A reported 2026 systematic review and meta-analysis estimated pooled

depressive symptoms at approximately 40% and anxiety symptoms at approximately 36% among adults with epilepsy [7].

A previous systematic review similarly reported mood and anxiety disorders as among the most common psychiatric comorbidities in adults with epilepsy [6].

Several mechanisms may contribute to this relationship. Persistent seizures may cause fear, functional restrictions, sleep disturbance, social isolation, and uncertainty about the future. Epilepsy-related stigma and employment limitations can also contribute to psychological distress.

There may be neurobiological links between epilepsy and psychiatric disorders, particularly in patients with focal epilepsy involving limbic networks. Importantly, the relationship is likely bidirectional rather than simply the result of seizures causing depression.

Depression and quality of life

The strongest association in the model was between depressive symptoms and quality of life. Patients with PHQ-9 scores of 10 or greater had markedly lower QOLIE-31 scores than patients without clinically significant depressive symptoms.

This observation is consistent with previous research showing that depression may have a greater influence on quality of life than seizure frequency in treatment-resistant epilepsy [11]. A systematic review of health-related quality-of-life determinants similarly identified depression as one of the most consistent predictors of impaired quality of life [12].

This has important clinical implications. A patient whose seizures remain frequent but whose depression is recognized and appropriately treated may experience meaningful improvement in functioning and quality of life even before complete seizure freedom is achieved.

Consequently, psychiatric screening should be considered part of comprehensive epilepsy care rather than an optional addition.

Anxiety and quality of life

Anxiety was also independently associated with reduced QOLIE-31 scores.

Patients with epilepsy may experience anticipatory anxiety concerning the next seizure, injury, social embarrassment, employment, driving restrictions, and medication failure. Anxiety may also increase attention to bodily sensations and seizure-related symptoms, potentially amplifying perceived disease burden.

Previous studies have demonstrated that anxiety contributes independently to reduced health-related quality of life in epilepsy [13]. The combination of depression and anxiety may be particularly detrimental because these conditions can reinforce one another and contribute to social withdrawal and impaired treatment engagement.

Antiseizure medication polytherapy

Most participants in the cohort were receiving polytherapy, reflecting the drug-resistant nature of the study population.

Participants receiving three or more ASMs demonstrated lower QOLIE-31 scores than those receiving one or two medications. This finding is consistent with systematic-review evidence in which most studies examining ASM number and quality of life reported poorer quality of life with increasing medication burden [5].

However, the interpretation requires caution. Patients who require three or more medications generally have more difficult-to-control epilepsy. Therefore, the observed association between ASM number and poor quality of life cannot automatically be interpreted as a direct pharmacological effect. Underlying disease severity may be a major confounder.

For this reason, the analysis adjusted for seizure frequency and other clinical characteristics. Even after adjustment, high

ASM burden remained independently associated with poorer quality of life in the model.

Medication adverse effects

Medication-related adverse effects were independently associated with poorer quality of life. This finding is clinically plausible because fatigue, dizziness, somnolence, cognitive slowing, irritability, and mood changes can directly interfere with daily activities.

The pharmacological effects of ASMs are heterogeneous. Some agents may be relatively neutral or potentially beneficial for mood, whereas others may contribute to psychiatric or behavioral symptoms in susceptible individuals.

Recent literature emphasizes the need to recognize psychiatric and behavioral adverse effects as part of individualized ASM selection and monitoring [14,15].

Medication review in drug-resistant epilepsy should therefore consider cognitive function, fatigue, sleep, mood, irritability, behavioral symptoms, social functioning, and overall treatment burden, in addition to seizure frequency.

Seizure frequency

Higher seizure frequency was independently associated with poorer quality of life. This is consistent with previous research demonstrating that seizure frequency is an important determinant of health-related quality of life [12].

Frequent seizures may restrict driving, employment, education, travel, and social activities. They may also increase fear of injury and dependence on caregivers.

Nevertheless, seizure frequency did not explain the entire burden of impaired quality of life. The simultaneous independent effects of depression, anxiety, medication burden, and adverse effects support a multidimensional model.

Pharmacotherapy and psychiatric management

The findings suggest that epilepsy treatment should be individualized beyond simple escalation of ASM number.

In patients with persistent seizures, clinicians should periodically assess whether each medication is providing meaningful seizure benefit relative to its adverse-effect burden. This does not mean that polytherapy should automatically be reduced. In drug-resistant epilepsy, combination therapy may be necessary.

Instead, the goal should be optimization of pharmacotherapy, balancing seizure control against tolerability, cognitive functioning, mood, and quality of life.

Where appropriate, referral to a comprehensive epilepsy center should be considered for patients fulfilling criteria for drug resistance, particularly when seizures persist despite appropriate medication trials. Potential non-pharmacological options may include epilepsy surgery evaluation, neurostimulation, dietary therapy, or other specialist interventions, depending on seizure type, epilepsy etiology, and individual suitability.

Clinical implications

The results support incorporating routine mental-health assessment into the management of drug-resistant epilepsy.

A practical clinical assessment could include:

- Seizure frequency and severity.
- Current ASM number and doses.
- Medication adverse effects.
- Depression screening.
- Anxiety screening.
- Quality-of-life assessment.
- Medication adherence.
- Assessment for epilepsy-surgery suitability where appropriate.

This approach may identify patients whose quality of life remains poor despite apparently appropriate neurological management.

Importantly, psychiatric screening tools such as PHQ-9 and GAD-7 are screening

instruments and should not replace comprehensive psychiatric assessment when clinically indicated.

Strengths

The study evaluates neurological, pharmacological, psychiatric, and patient-reported outcomes simultaneously. It focuses specifically on adults with drug-resistant epilepsy and assesses ASM burden separately from seizure frequency.

Both depression and anxiety are evaluated using standardized instruments, while quality of life is assessed using a disease-specific epilepsy instrument. Multivariable analysis allows adjustment for important clinical confounders.

The study provides a multidisciplinary framework suitable for neurology, clinical pharmacology, psychiatry, and rehabilitation research.

Limitations

First, the cross-sectional design prevents determination of temporal or causal relationships.

Second, patients receiving multiple ASMs may have more severe epilepsy, creating confounding by indication.

Third, PHQ-9 and GAD-7 are screening instruments rather than diagnostic psychiatric interviews.

Fourth, medication adverse effects were based partly on patient reporting and may therefore be subject to recall or attribution bias.

Fifth, ASM number does not fully capture pharmacological exposure because medications differ in dose, pharmacokinetics, mechanism, interactions, and adverse-effect profiles.

Sixth, quality of life may be influenced by socioeconomic status, employment, stigma, family support, and access to specialist care.

Seventh, the study was designed as a single-center hospital-based investigation, potentially limiting generalizability.

Finally, the numerical findings presented in this manuscript are and must not be presented as actual clinical observations.

Conclusion

Adults with drug-resistant epilepsy may experience substantial psychiatric and quality-of-life burden in addition to persistent seizures.

In the analysis, depression and anxiety were strongly associated with poorer epilepsy-specific quality of life. Greater ASM burden, frequent seizures, and clinically significant medication adverse effects were also independently associated with lower quality-of-life scores.

These findings support a multidimensional model of epilepsy care in which treatment success is assessed not only by seizure reduction but also by psychiatric well-being, medication tolerability, cognitive and functional status, and patient-reported quality of life.

Routine screening for depression and anxiety, periodic review of ASM burden and adverse effects, and referral for comprehensive epilepsy management may help identify modifiable contributors to poor outcomes.

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