

Research Article

Association of Levetiracetam Exposure With Behavioral Symptoms, Depression, Anxiety, and Medication Adherence Among Adults With Epilepsy: A Cross-Sectional Study

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Abstract

Background: Levetiracetam is widely used in the pharmacological management of epilepsy because of its broad antiseizure efficacy, relatively favorable pharmacokinetic profile, and limited potential for pharmacokinetic drug interactions. However, behavioral and psychiatric adverse effects, including irritability, aggression, agitation, depression, and anxiety, have been reported and may compromise treatment tolerability and adherence. This study evaluated the association between levetiracetam exposure and behavioral symptoms, depression, anxiety, and medication adherence among adults with epilepsy.

Methods: This hospital-based cross-sectional study included 240 adults with epilepsy receiving stable antiseizure pharmacotherapy. Participants were categorized according to current levetiracetam exposure. Levetiracetam dose, treatment duration, concomitant antiseizure medications, seizure frequency, previous psychiatric history, and medication-related

adverse effects were documented. Behavioral symptoms were assessed using a structured behavioral adverse-effect checklist. Depressive and anxiety symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), respectively. Medication adherence was assessed using the 8-item Morisky Medication Adherence Scale (MMAS-8). Multivariable logistic regression was used to identify independent predictors of clinically significant behavioral symptoms, depression, anxiety, and low medication adherence.

Results: In the illustrative cohort, 128 participants (53.3%) were receiving levetiracetam and 112 (46.7%) were receiving other antiseizure medications without levetiracetam. Behavioral symptoms were reported by 31.3% of levetiracetam-exposed participants compared with 15.2% of non-exposed participants ($p = 0.003$). Irritability, agitation, emotional lability, and aggression were the most frequently reported behavioral manifestations. Clinically significant depressive symptoms were

present in 37.5% of levetiracetam-exposed participants compared with 25.0% of non-exposed participants. Clinically significant anxiety symptoms were present in 32.8% and 21.4%, respectively. Low medication adherence was observed in 35.2% of levetiracetam-exposed participants compared with 20.5% of non-exposed participants. After adjustment for age, sex, epilepsy duration, seizure frequency, previous psychiatric history, number of antiseizure medications, and treatment duration, levetiracetam exposure remained independently associated with behavioral symptoms (adjusted odds ratio [aOR] 2.08, 95% confidence interval [CI] 1.14–3.79; $p = 0.017$) and low medication adherence (aOR 1.91, 95% CI 1.03–3.53; $p = 0.040$). Behavioral symptoms were also strongly associated with low adherence.

Conclusion: Levetiracetam exposure was associated with increased behavioral symptoms and lower medication adherence in the illustrative cohort. Depression and anxiety were also more frequent among exposed patients, although these associations may be influenced by underlying psychiatric and epilepsy-related factors. Routine assessment of behavioral and psychiatric symptoms may help identify patients at risk of poor tolerability and non-adherence during levetiracetam therapy.

Keywords: Levetiracetam, epilepsy, behavioral adverse effects, irritability, depression, anxiety, medication adherence, antiseizure medication, pharmacovigilance, neurology.

Introduction

Epilepsy is a chronic neurological disorder requiring long-term pharmacological treatment in most affected individuals. Antiseizure medications remain the principal treatment for reducing seizure recurrence. The selection of an appropriate medication depends on seizure type, epilepsy syndrome, comorbidities, drug interactions, tolerability,

reproductive considerations, and individual patient characteristics.

Levetiracetam is one of the most frequently used modern antiseizure medications. Its widespread clinical use is related to broad-spectrum antiseizure activity, relatively simple dosing, rapid and predictable absorption, predominantly renal elimination, and limited hepatic drug interactions.

Levetiracetam differs pharmacologically from many traditional antiseizure medications because its principal molecular target is synaptic vesicle protein 2A (SV2A). Binding to SV2A is believed to modify neurotransmitter release and contribute to its antiseizure activity.

Despite its favorable pharmacokinetic characteristics, levetiracetam has attracted considerable attention because of its neuropsychiatric and behavioral adverse effects.

Behavioral manifestations reported during levetiracetam therapy include irritability, agitation, anger, hostility, aggression, emotional lability, and mood changes. More severe manifestations, such as psychosis, suicidal behavior, or severe psychiatric disturbances, have also been described, although these events are substantially less common.

An early systematic review of adult clinical trials reported depression, nervousness, hostility, anxiety, and emotional lability among behavioral events associated with levetiracetam [1]. More recent evidence continues to demonstrate that neuropsychiatric manifestations are an important consideration during levetiracetam therapy. A retrospective study involving 1,412 patients reported severe psychiatric symptoms in 7.8% of levetiracetam-treated patients, with hallucinations, delusions, aggressive behavior, and agitation among the reported manifestations [2].

However, the relationship between levetiracetam and psychiatric symptoms is not straightforward.

Patients with epilepsy may already have an increased baseline risk of depression and anxiety. Psychiatric history is also an important predictor of behavioral adverse effects during antiseizure medication therapy. Research involving newer antiseizure medications has identified psychiatric history as an important predictor of psychiatric and behavioral side effects [3].

Therefore, observing a higher prevalence of depression or anxiety among levetiracetam users does not establish that levetiracetam caused these symptoms.

A population-based study published in 2019 further demonstrated that pre-existing depression and anxiety were important predictors of psychiatric symptoms following levetiracetam initiation [4]. These findings emphasize the importance of assessing baseline psychiatric vulnerability when investigating levetiracetam-associated behavioral effects.

Medication adherence represents another clinically important component.

Epilepsy requires sustained adherence to antiseizure medication therapy because missed doses may increase the risk of breakthrough seizures. Adverse effects, complex treatment schedules, negative beliefs about medications, forgetfulness, cost, and inadequate understanding of the disease may all contribute to non-adherence. Behavioral or psychiatric adverse effects may represent a particularly important but underrecognized pathway to poor adherence. Patients who experience irritability, mood changes, agitation, or other distressing symptoms may intentionally reduce doses, skip medications, or discontinue treatment without medical advice.

Evidence from earlier levetiracetam studies suggests that behavioral abnormalities can be sufficiently severe to require dose reduction

or treatment discontinuation. In a case-control study of 553 patients, 6.9% discontinued levetiracetam because of behavioral abnormalities. Faster titration and previous psychiatric disorders were among the factors associated with discontinuation [5].

Recent reviews similarly emphasize irritability, aggression, and agitation as clinically relevant behavioral adverse effects and recommend early recognition and appropriate management [6].

A systematic review and meta-analysis published in 2026 further examined neuropsychiatric adverse events associated with antiseizure medications and reported differences in psychiatric and behavioral outcomes between medications [7].

Nevertheless, the available literature remains heterogeneous with respect to patient populations, outcome definitions, baseline psychiatric status, levetiracetam dose, treatment duration, concomitant medications, and comparator groups.

There is therefore a need for studies that simultaneously assess levetiracetam exposure, behavioral symptoms, depression, anxiety, treatment adherence, seizure frequency, and previous psychiatric history.

The present study was designed to evaluate these relationships among adults with epilepsy receiving routine antiseizure pharmacotherapy.

Objectives

Primary Objective

To determine the association between levetiracetam exposure and clinically significant behavioral symptoms among adults with epilepsy.

Secondary Objectives

1. To compare depressive and anxiety symptoms between levetiracetam-exposed and non-exposed patients.
2. To determine the association between levetiracetam exposure and medication adherence.

3. To evaluate whether levetiracetam dose and duration of therapy are associated with behavioral or psychiatric symptoms.
4. To identify independent predictors of low medication adherence.

Materials and Methods

Study Design

A hospital-based cross-sectional observational study was designed to evaluate the relationship between levetiracetam exposure and behavioral, psychiatric, and medication-adherence outcomes in adults with epilepsy at Isra University.

Study Setting

The study was conducted at Isra University.

Study Duration

An study duration of 18 months was used.

Study Population

Adults with an established diagnosis of epilepsy who were receiving maintenance antiseizure medication therapy were eligible. Participants were divided into two principal groups.

Group A: Levetiracetam-exposed. Patients currently receiving levetiracetam as part of their antiseizure regimen.

Group B: Non-levetiracetam group. Patients receiving other antiseizure medications without current levetiracetam exposure.

The comparator group was included to distinguish symptoms associated with levetiracetam exposure from psychiatric and behavioral symptoms occurring as part of epilepsy itself.

Inclusion Criteria

Participants were eligible if they:

1. Were aged 18 years or older.
2. Had a clinically established diagnosis of epilepsy.
3. Were receiving maintenance antiseizure medication.
4. Had been receiving their current principal antiseizure medication regimen for at least four weeks.

5. Had sufficient cognitive capacity to complete study questionnaires.
6. Provided informed consent.

Exclusion Criteria

Patients were excluded if they:

1. Had acute symptomatic seizures without established epilepsy.
2. Were experiencing status epilepticus at the time of assessment.
3. Had severe cognitive impairment preventing reliable questionnaire completion.
4. Had an acute psychotic episode requiring immediate psychiatric hospitalization.
5. Had a major neurological disease independently affecting behavioral assessment.
6. Had incomplete medication information.
7. Had initiated or discontinued levetiracetam within the preceding four weeks.

Clinical Data Collection

A standardized proforma was used to record age, sex, education, employment, epilepsy duration, age at epilepsy onset, seizure type, seizure frequency, history of generalized tonic-clonic seizures, history of status epilepticus, epilepsy etiology where known, current antiseizure medications, number of antiseizure medications, levetiracetam dose, levetiracetam treatment duration, recent dose changes, previous psychiatric history, current psychiatric medication, self-reported medication adverse effects, and history of antiseizure medication discontinuation because of adverse effects.

Assessment of Levetiracetam Exposure

For patients receiving levetiracetam, daily dose and treatment duration were documented.

Daily dose: Daily levetiracetam dose was recorded in milligrams per day. For exploratory analysis, exposure was

categorized as less than 1,000 mg/day, 1,000–1,999 mg/day, and 2,000 mg/day or more.

Treatment duration: Duration of levetiracetam exposure was recorded in months. For exploratory analysis, treatment duration was categorized as less than six months, six to 24 months, and more than 24 months.

Dose and duration categories should be modified according to the actual distribution of the study population.

Assessment of Behavioral Symptoms

Behavioral adverse effects were assessed using a structured symptom checklist developed from previously described levetiracetam-associated behavioral manifestations.

The following symptoms were evaluated: irritability, anger, aggression, agitation, hostility, emotional lability, nervousness, impulsivity, mood instability, personality change, social withdrawal, hyperactivity, suicidal thoughts, and psychotic symptoms. Participants rated symptoms as absent, mild, moderate, or severe.

A clinically significant behavioral symptom was defined as a moderate or severe symptom that was new, worsened during therapy, or interfered with daily functioning.

This approach is consistent with the clinical literature describing irritability, aggression, agitation, and mood changes as important behavioral adverse effects of levetiracetam [1,6].

Assessment of Depression

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

Severity was categorized as follows: 0–4, minimal; 5–9, mild; 10–14, moderate; 15–19, moderately severe; and 20–27, severe.

A score of 10 or higher was considered indicative of clinically significant depressive symptoms.

The questionnaire was used as a screening measure and not as a substitute for formal psychiatric diagnosis.

Assessment of Anxiety

Anxiety symptoms were assessed using the Generalized Anxiety Disorder-7 questionnaire.

Severity was categorized as follows: 0–4, minimal; 5–9, mild; 10–14, moderate; and 15–21, severe.

A score of 10 or higher was considered indicative of clinically significant anxiety symptoms.

Assessment of Medication Adherence

Medication adherence was evaluated using the 8-item Morisky Medication Adherence Scale.

Participants were categorized as having high, medium, or low adherence according to the instrument's scoring framework.

For regression analysis, low adherence was considered the primary adverse adherence outcome.

Where feasible, self-reported adherence should be supplemented by pharmacy refill records, pill counts, or prescription records.

Assessment of Seizure Frequency

Seizure frequency during the preceding three months was recorded from patient diaries, caregiver reports, and clinical records where available.

For analysis, patients were categorized as having no seizures during the preceding three months, one to three seizures per month, or four or more seizures per month.

The seizure-frequency variable was included as a potential confounder because seizure burden may independently contribute to depression, anxiety, and poor medication adherence.

Previous Psychiatric History

Previous psychiatric history was defined as a documented diagnosis or clinically treated episode of depression, anxiety disorder, bipolar disorder, psychotic disorder, personality disorder, or previous suicidal behavior.

Previous psychiatric history was incorporated into the regression model

because it is an important potential confounder and risk factor for behavioral adverse effects during levetiracetam therapy [3–5].

Outcome Measures

Primary outcome: Clinically significant behavioral symptoms.

Secondary outcomes: PHQ-9 score, GAD-7 score, clinically significant depressive symptoms, clinically significant anxiety symptoms, medication adherence category, self-reported medication discontinuation or dose reduction, association of levetiracetam dose with behavioral symptoms, and association of levetiracetam treatment duration with behavioral symptoms.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Continuous variables were presented as mean and standard deviation or median and interquartile range. Categorical variables were presented as frequencies and percentages.

The independent-samples t-test or Mann–Whitney U test was used for continuous variables according to data distribution. The chi-square test or Fisher's exact test was used for categorical variables.

Correlation between levetiracetam dose and psychiatric symptom scores was assessed using Pearson or Spearman correlation, as appropriate.

Multivariable logistic regression was performed to identify independent predictors of clinically significant behavioral symptoms. A second regression model was used to identify independent predictors of low medication adherence.

Potential confounders included age, sex, epilepsy duration, seizure frequency, number of antiseizure medications, previous psychiatric history, levetiracetam exposure, levetiracetam dose, and levetiracetam treatment duration.

Adjusted odds ratios with 95% confidence intervals were reported.

A p-value below 0.05 was considered statistically significant.

Results

The following results are and must be replaced with actual patient-level data before publication.

Baseline Characteristics

A total of 240 adults with epilepsy were included in the analysis. Of these, 128 participants (53.3%) were receiving levetiracetam and 112 (46.7%) were receiving other antiseizure medications without levetiracetam.

The mean age of the cohort was 35.9 ± 12.1 years. The two groups were broadly comparable in age, sex, epilepsy duration, and seizure type

Table 1. Baseline Clinical and Treatment Characteristics

Characteristic	Levetiracetam (n = 128)	Non-LEV (n = 112)	p-value
Age, years	35.4 ± 11.9	36.5 ± 12.3	0.47
Male sex	72 (56.3%)	59 (52.7%)	0.58
Epilepsy duration, years	12.4 ± 8.1	11.8 ± 7.6	0.55
Focal epilepsy	79 (61.7%)	69 (61.6%)	0.99
Generalized epilepsy	34 (26.6%)	29 (25.9%)	0.91

Characteristic	Levetiracetam (n = 128)	Non-LEV (n = 112)	p-value
Other or combined epilepsy	15 (11.7%)	14 (12.5%)	0.86
Four or more seizures per month	55 (43.0%)	43 (38.4%)	0.48
ASM polytherapy	74 (57.8%)	62 (55.4%)	0.71
Previous psychiatric history	25 (19.5%)	18 (16.1%)	0.49
Mean number of ASMs	1.9 ± 0.8	1.7 ± 0.7	0.04

Behavioral Symptoms

Behavioral symptoms were more frequently reported among levetiracetam-exposed participants. Overall, 40 levetiracetam-exposed patients (31.3%) reported at least one clinically significant behavioral symptom compared with 17 patients (15.2%) in the non-levetiracetam group.

Irritability was the most common behavioral manifestation, followed by agitation, emotional lability, and aggression.

Table 2. Behavioral Symptoms According to Levetiracetam Exposure

Behavioral symptom	Levetiracetam, n (%)	Non-LEV, n (%)	p-value
Any clinically significant behavioral symptom	40 (31.3%)	17 (15.2%)	0.003
Irritability	31 (24.2%)	12 (10.7%)	0.006
Agitation	18 (14.1%)	6 (5.4%)	0.028
Emotional lability	15 (11.7%)	5 (4.5%)	0.046
Aggression or hostility	12 (9.4%)	4 (3.6%)	0.079
Anger	13 (10.2%)	5 (4.5%)	0.091
Nervousness	11 (8.6%)	5 (4.5%)	0.20
Social withdrawal	8 (6.3%)	5 (4.5%)	0.57
Severe behavioral symptoms	7 (5.5%)	2 (1.8%)	0.17

Depression, Anxiety, and Medication Adherence

The levetiracetam group demonstrated higher mean PHQ-9 and GAD-7 scores.

Clinically significant depression was identified in 48 levetiracetam-exposed patients (37.5%) compared with 28 non-exposed patients (25.0%). Low medication adherence was also more frequent among levetiracetam users.

Table 3. Depression, Anxiety, and Medication Adherence

Outcome	Levetiracetam (n = 128)	Non-LEV (n = 112)	p-value
Mean PHQ-9 score	8.9 ± 6.3	6.9 ± 5.5	0.009
PHQ-9 score ≥ 10	48 (37.5%)	28 (25.0%)	0.041
Mean GAD-7 score	7.8 ± 5.8	5.9 ± 5.0	0.008
GAD-7 score ≥ 10	42 (32.8%)	24 (21.4%)	0.048
High adherence	39 (30.5%)	43 (38.4%)	Not reported
Medium adherence	44 (34.4%)	46 (41.1%)	Not reported
Low adherence	45 (35.2%)	23 (20.5%)	0.019
Self-reported missed doses	51 (39.8%)	28 (25.0%)	0.018
Dose reduction without medical advice	14 (10.9%)	6 (5.4%)	0.13
Treatment discontinuation because of adverse effects	8 (6.3%)	3 (2.7%)	0.23

Dose and Duration of Levetiracetam Exposure

Within the levetiracetam group, behavioral symptoms were more frequently observed among patients receiving higher daily doses.

The prevalence of clinically significant behavioral symptoms increased from 22.0% among patients receiving less than 1,000 mg/day to 40.0% among those receiving 2,000 mg/day or more.

Table 4. Behavioral Symptoms According to Levetiracetam Dose and Duration

Exposure category	Behavioral symptoms, n (%)	Depression, n (%)	Anxiety, n (%)
Less than 1,000 mg/day	9/41 (22.0%)	12/41 (29.3%)	10/41 (24.4%)
1,000–1,999 mg/day	16/52 (30.8%)	19/52 (36.5%)	16/52 (30.8%)

Exposure category	Behavioral symptoms, n (%)	Depression, n (%)	Anxiety, n (%)
2,000 mg/day or more	14/35 (40.0%)	17/35 (48.6%)	15/35 (42.9%)
p for trend	0.041	0.071	0.058

For treatment duration, behavioral symptoms were reported in 10 of 35 patients (28.6%) receiving levetiracetam for less than six months, 18 of 57 patients (31.6%) receiving treatment for six to 24 months, and 12 of 36 patients (33.3%) receiving treatment for more than 24 months.

Treatment duration	Behavioral symptoms, n (%)
Less than 6 months	10/35 (28.6%)
6–24 months	18/57 (31.6%)
More than 24 months	12/36 (33.3%)

Independent Predictors of Behavioral Symptoms

After adjustment for age, sex, seizure frequency, epilepsy duration, number of antiseizure medications, and psychiatric history, levetiracetam exposure remained independently associated with clinically significant behavioral symptoms.

Previous psychiatric history was also a strong predictor.

Table 5. Multivariable Logistic Regression for Clinically Significant Behavioral Symptoms

Predictor	Adjusted OR	95% CI	p-value
Levetiracetam exposure	2.08	1.14–3.79	0.017
Previous psychiatric history	2.91	1.45–5.84	0.003
Four or more seizures per month	1.69	0.96–2.98	0.069
ASM polytherapy	1.43	0.81–2.53	0.215
Epilepsy duration greater than 10 years	1.18	0.67–2.08	0.568
Male sex	1.16	0.67–2.01	0.591

Independent Predictors of Low Medication Adherence

Behavioral symptoms demonstrated the strongest association with low adherence. Levetiracetam exposure also remained independently associated with low adherence after adjustment.

Table 6. Multivariable Logistic Regression for Low Medication Adherence

Predictor	Adjusted OR	95% CI	p-value
Levetiracetam exposure	1.91	1.03–3.53	0.040
Clinically significant behavioral symptoms	2.87	1.49–5.52	0.002
Depression (PHQ-9 $\geq$ 10)	1.78	0.98–3.24	0.058
Anxiety (GAD-7 $\geq$ 10)	1.49	0.80–2.78	0.210
Four or more seizures per month	1.64	0.91–2.94	0.099
ASM polytherapy	1.38	0.77–2.47	0.279

Discussion

The present study investigated whether levetiracetam exposure was associated with behavioral symptoms, depression, anxiety, and medication adherence among adults with epilepsy.

The main finding was that levetiracetam-exposed patients had a higher frequency of clinically significant behavioral symptoms than patients receiving other antiseizure medications. Irritability was the most frequent manifestation, followed by agitation and emotional lability.

Levetiracetam exposure was also associated with higher depressive and anxiety symptom scores and lower medication adherence. However, the association between levetiracetam and psychiatric symptoms should be interpreted carefully because epilepsy itself and pre-existing psychiatric illness can independently produce these symptoms.

Behavioral Effects of Levetiracetam

Behavioral abnormalities are among the most recognized adverse effects associated with levetiracetam.

An early systematic review of clinical trials involving adults reported depression, nervousness, hostility, anxiety, and emotional lability among behavioral events observed during levetiracetam therapy [1].

More recent evidence continues to support this association. A 2024 study of 1,412 levetiracetam-treated patients identified severe psychiatric symptoms in 7.8% of participants, with hallucinations, delusions, aggression, and agitation among the reported manifestations [2].

A recent review also summarized irritability, anger, and aggression as common behavioral manifestations and emphasized the importance of early recognition [6].

The prevalence in this study is clinically plausible, although actual prevalence varies considerably according to population, outcome definition, baseline psychiatric status, and study methodology.

Irritability as the Predominant Behavioral Manifestation

Irritability was the most common behavioral symptom in the cohort.

This is consistent with the broader literature, in which irritability is repeatedly described as a characteristic behavioral adverse effect of levetiracetam.

Mild irritability may be overlooked during routine neurological follow-up. Patients may not spontaneously describe a change in temperament as a medication adverse effect, and clinicians may attribute irritability to psychosocial stress or the underlying epilepsy.

A structured adverse-effect assessment may therefore improve recognition.

Previous Psychiatric History

Previous psychiatric illness was one of the strongest predictors of behavioral symptoms. This finding is consistent with previous evidence demonstrating that patients with a history of psychiatric disorders are more susceptible to psychiatric and behavioral adverse effects during antiseizure medication therapy [3–5].

A prediction study of patients receiving levetiracetam found that previous depression and anxiety were significant predictors of subsequent psychiatric symptoms [4].

Before initiating levetiracetam, clinicians may consider documenting previous depression, anxiety disorders, aggressive behavior, bipolar disorder, psychosis, suicidal ideation or behavior, and previous antiseizure medication-related behavioral reactions.

Patients with such histories may benefit from closer monitoring after treatment initiation or dose escalation.

Depression

Depressive symptoms were more common in the levetiracetam group. However, this association should not automatically be interpreted as evidence that levetiracetam causes depression.

Patients with epilepsy have a higher baseline prevalence of depression than the general population. Depression can also be associated with seizure frequency, disease duration, psychosocial stress, stigma, and treatment burden.

The 2026 systematic review of levetiracetam-related neuropsychiatric effects reported that depression was commonly described across studies, but comparisons between levetiracetam and other antiseizure medications did not consistently demonstrate a statistically significant excess risk [7].

Therefore, the cross-sectional association observed in this study should be interpreted

as an association rather than proof of causality.

Anxiety

Anxiety symptoms were also more common among levetiracetam-exposed participants.

Recent evidence suggests that anxiety may occur as part of the neuropsychiatric adverse-effect profile of levetiracetam, although findings are heterogeneous [7].

Anxiety may also be driven by fear of seizures, restrictions on driving and employment, social stigma, and uncertainty regarding disease control.

For this reason, adjustment for seizure frequency and previous psychiatric history is important when assessing the independent contribution of levetiracetam.

Levetiracetam Dose

The analysis demonstrated a dose-related increase in behavioral symptoms.

A dose-response relationship would strengthen the pharmacological interpretation if demonstrated in a real dataset, although it should not be assumed.

Previous evidence has identified titration rate and psychiatric vulnerability as important factors in behavioral tolerability. A case-control study found that faster titration to the maximum dose and previous psychiatric disorders were associated with levetiracetam discontinuation because of behavioral abnormalities [5].

Therefore, the relationship between dose and behavior may be influenced not only by absolute daily dose but also by the speed of dose escalation and individual susceptibility.

Medication Adherence

One clinically important finding of this study was the association between levetiracetam exposure and lower medication adherence.

This relationship may occur through several pathways. Behavioral symptoms may make patients reluctant to continue treatment. Depression and anxiety may reduce motivation and consistency with chronic medication use. Patients experiencing

adverse effects may intentionally skip doses or reduce their dose.

The strong association between behavioral symptoms and low adherence in the regression model supports the possibility that tolerability may be an important pathway linking levetiracetam exposure to treatment non-adherence.

However, adherence is multifactorial. It is also influenced by medication cost, dosing frequency, forgetfulness, health literacy, family support, seizure beliefs, perceived medication effectiveness, access to healthcare, and treatment complexity.

Therefore, levetiracetam should not be considered the sole determinant of adherence.

Clinical Pharmacological Implications

The findings have practical implications for individualized antiseizure medication selection.

Levetiracetam has several important advantages, including convenient pharmacokinetics and relatively limited drug-drug interactions. Consequently, the potential for behavioral adverse effects does not mean that levetiracetam should be avoided universally.

Clinicians should balance seizure efficacy, tolerability, psychiatric vulnerability, adherence, and patient preference.

In a patient who achieves excellent seizure control with levetiracetam but develops mild irritability, careful monitoring and dose adjustment may be appropriate.

In a patient who develops severe aggression, psychosis, suicidal symptoms, or substantial functional deterioration, urgent clinical reassessment is warranted and alternative treatment may need to be considered.

This individualized approach is particularly important because the literature demonstrates considerable inter-individual variability in susceptibility.

Behavioral Symptoms and Treatment Discontinuation

Previous studies have demonstrated that behavioral symptoms may be severe enough to require levetiracetam dose reduction or discontinuation.

In the study by White and colleagues, 6.9% of 553 patients discontinued levetiracetam because of behavioral abnormalities [5].

Studies of psychiatric and behavioral adverse effects across newer antiseizure medications have also reported clinically relevant behavioral tolerability concerns with levetiracetam compared with several alternative medications [3].

These findings suggest that behavioral tolerability should be incorporated into routine medication review rather than considered an unusual complication.

Strengths

The study specifically evaluates levetiracetam rather than grouping all antiseizure medications together.

A non-levetiracetam comparison group is included.

Behavioral symptoms, depression, anxiety, and adherence are evaluated simultaneously. Levetiracetam dose and treatment duration are considered.

Previous psychiatric history is explicitly incorporated as a confounding variable.

Seizure frequency and antiseizure medication polytherapy are considered in multivariable analysis.

The study has direct relevance to clinical pharmacology and individualized antiseizure medication selection.

Limitations

First, the cross-sectional design prevents definitive assessment of causality.

Second, baseline psychiatric status before levetiracetam initiation may not be available in all patients.

Third, the PHQ-9 and GAD-7 identify symptoms rather than establish formal psychiatric diagnoses.

Fourth, medication adherence was assessed primarily through self-report and may

therefore be affected by recall and social-desirability bias.

Fifth, patients receiving levetiracetam may differ systematically from those receiving other antiseizure medications because of seizure type, treatment history, or clinician prescribing preference.

Sixth, concomitant antiseizure medication therapy may influence psychiatric symptoms and cannot always be completely separated from levetiracetam exposure.

Seventh, the study did not assess genetic or pharmacogenomic susceptibility to levetiracetam-related behavioral adverse effects.

Finally, the numerical results in this manuscript are and must be replaced with real data before submission.

Conclusion

Levetiracetam exposure was associated with a higher frequency of clinically significant behavioral symptoms and lower medication adherence in the adult epilepsy cohort. Irritability, agitation, and emotional lability were the predominant behavioral manifestations.

Depressive and anxiety symptoms were also more frequent among levetiracetam-exposed patients, although these relationships are likely influenced by underlying epilepsy characteristics and pre-existing psychiatric vulnerability.

Previous psychiatric history emerged as an important predictor of behavioral symptoms, while behavioral adverse effects were strongly associated with poor medication adherence.

These findings support routine assessment of behavioral and psychiatric symptoms during levetiracetam therapy, particularly after treatment initiation or dose escalation and in patients with previous psychiatric illness.

Individualized antiseizure medication selection should balance seizure control with behavioral tolerability and treatment adherence.

Declarations

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