



Behavioral Adverse Effects of Levetiracetam in Children with Epilepsy: A Longitudinal Study in Mofid Children's Hospital

Running Title: Levetiracetam Behavioral Effects in Children

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Abstract

Background and Objectives: Epilepsy is one of the most common chronic neurological disorders in childhood and is associated with behavioral comorbidities such as attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). Levetiracetam (LEV), a broad-spectrum antiepileptic drug, has gained popularity for pediatric use due to its favorable pharmacokinetic profile. However, its behavioral side effects remain a concern, with inconsistent findings across studies. This study aimed to determine the incidence and pattern of behavioral and mood disorders following LEV administration in children with epilepsy.

Materials and Methods: In this longitudinal study, 77 children aged over three years with epilepsy who referred to Mofid Children's Hospital, Tehran, from March 2024 to March 2025 were evaluated. Behavioral symptoms, including Hyperactivity, ODD, and sleep disturbances, were assessed according to the DSM-5 criteria before and six months after starting LEV therapy. Data were analyzed using SPSS version 24, employing chi-square and t-tests for comparison.

Results: The mean age of participants was 7.16 ± 3.24 years. After six months of LEV therapy, DSM-5 behavioral scores significantly increased ($p < 0.001$). Following six months of treatment, the proportion of children exhibiting irritability, impulsivity, and restlessness nearly tripled, increasing from 10.4%, 6.5%, and 5.2% to 27.3%, 16.9%, and 16.9%, respectively. Sleep disturbances also slightly increased.

Conclusion: Levetiracetam usage was significantly associated with increased behavioral symptoms, particularly Hyperactivity- and ODD-related features. Careful behavioral monitoring is recommended during LEV therapy to ensure early detection and individualized management.

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Introduction

Epilepsy is one of the most prevalent chronic neurological disorders in childhood and represents a major global public health challenge. It is defined as a tendency toward recurrent, unprovoked seizures resulting from abnormal cortical neuronal activity. According to the World Health Organization, approximately 50 million people worldwide are affected, with nearly half being children. The prevalence in pediatric populations ranges between 0.5% and 1%, increasing to nearly 1.5% in developing countries due to limited access to medical care and higher rates of perinatal complications (1, 2). In Iran, epilepsy affects about 0.5% of the population, nearly 4 million people nationally (3).

Recurrent seizures in childhood can have profound consequences for cognitive, emotional, and behavioral development. Children with epilepsy often experience behavioral disturbances, learning difficulties, and social maladjustment at higher rates than their healthy peers (1, 4). Among these, attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) are the most frequently reported behavioral comorbidities, reducing quality of life and complicating seizure control and treatment adherence (5).

Pharmacotherapy remains the cornerstone of epilepsy management, and antiepileptic drugs (AEDs) have evolved substantially over recent decades. Among newer generation AEDs, Levetiracetam (LEV) has become a mainstay therapy for both focal and generalized seizures in children. Introduced in 1999, LEV is characterized by predictable pharmacokinetics, minimal hepatic metabolism, limited drug interactions, and rapid oral absorption. It acts primarily through binding to the synaptic vesicle protein 2A (SV2A), thereby stabilizing neuronal excitability (5, 6).

Despite these favorable properties, emerging evidence suggests that LEV may induce or exacerbate behavioral and emotional side effects in children, including irritability, aggression, anxiety, mood swings, and sleep disturbances. Reported incidence rates vary widely, from 10% to 38%, with a meta-analysis indicating irritability in 23–34% and aggression in 15–28% of pediatric patients (7). Although usually mild to moderate, 5–15% of cases may require discontinuation of the medication, risking seizure recurrence (8, 9). The mechanisms remain incompletely understood, with proposed explanations including disruption of GABAergic and glutamatergic balance, modulation of serotonin and dopamine pathways, and altered limbic and prefrontal signaling.

Several studies have explored LEV's behavioral impact with mixed results. In Iran, despite extensive LEV use, systematic research investigating its behavioral side effects in local pediatric populations is lacking. Mofid Children's Hospital, as a major tertiary referral center, provides a unique setting for such investigations. This study was designed to determine the incidence and pattern of behavioral disorders following LEV therapy in children over three years of age, identify potential risk factors, explore associations between LEV dosage and behavioral changes, and assess the influence of these side effects on treatment outcomes, ultimately guiding safer and more individualized therapeutic strategies.

Materials and Methods

Study Design and Setting

This descriptive longitudinal study was conducted at Mofidi Children's Hospital, Tehran, Iran, from March 2024 to March 2025, to evaluate behavioral and mood effects of Levetiracetam (LEV) in children aged 3–17 years with seizure disorders. The longitudinal design allowed within-subject comparison of behavioral symptoms before and six months after LEV therapy. Ethical approval was obtained from Shahid Beheshti

University of Medical Sciences, and written informed consent was provided by parents or guardians.

Participants and Sampling

Children referred for seizure management and indicated for LEV therapy were recruited via convenience sampling until a sample of 77 was reached. Sample size was calculated based on a 23.3% incidence of LEV-related behavioral changes (10), with 90% confidence, 70% power, and 10% margin of error. Inclusion criteria were age >3 years, clinical epilepsy diagnosis per ILAE criteria, LEV indication, absence of major psychiatric disorder, and parental consent. Exclusion criteria included concomitant treatment with other anti-seizure medications (ASMs), a prior psychiatric or developmental disorder that had led to parental concern and medical consultation, discontinuation of Levetiracetam before six months, or incomplete data Study Procedure After enrollment, participants underwent history taking, neurological examination, and record review. Baseline demographic and clinical data were collected. Levetiracetam dosing was individualized according to clinical judgment, starting at a mean of 20 mg/kg/day and titrated to 40 mg/kg/day in two divided daily doses. Behavioral and mood reassessment was conducted after six months using the same DSM-5-based instrument.

Behavioral Assessment

Behavioral symptoms were assessed using a Persian-validated DSM-5 questionnaire through parental reports and clinical observation. The evaluated domains included hyperactivity, oppositional defiant disorder (ODD), and sleep disturbances.

Definitions of assessed behavioral traits were based on validated literature as follows:

- Irritability: a heightened tendency to experience anger or frustration in response to minor stimuli (11).
- Impulsivity: the tendency to act quickly without adequate thought or consideration of consequences (12).
- Restlessness: an inability to remain still, often manifested by excessive movement or agitation (13).
- Anxiety/Mood changes: emotional instability characterized by excessive worry or fluctuating affective states (14).
- Sleep disturbance: difficulty in initiating or

maintaining sleep or non-restorative sleep causing daytime impairment (15).

- Oppositional defiant traits: a persistent pattern of negativistic, disobedient, or hostile behavior toward authority figures (16).

Responses were rated on a three-point Likert scale:

0 = “never,” 1 = “sometimes” (approximately 1–3 days/week), and 2 = “often” (≥ 4 days/week or daily). For each participant, the total behavioral score ranged from 0 to 14. Domain-specific scores were calculated at baseline and at six months, with differences reflecting LEV-related changes. Hyperactivity was defined as a score ≥ 6 in inattention or hyperactivity–impulsivity items, ODD as ≥ 4 symptoms persisting ≥ 6 months, and sleep disturbance as persistent insomnia, sleep latency > 30 min, or daytime somnolence ≥ 3 times/week.

Clinical and Demographic Variables

Collected variables included age, sex, seizure onset age, seizure type, EEG pattern, perinatal complications, family history of epilepsy/hyperactivity, mode of delivery, metabolic/genetic disorders, and history of traumatic brain injury. Behavioral outcomes were recorded categorically and quantitatively.

Data Management and Quality Control

Trained pediatric residents administered questionnaires and recorded data, which were entered into SPSS v24 with anonymized identifiers. Quality measures included interviewer training, validated instruments (Cronbach's $\alpha = 0.84$), pilot testing, random verification of 10% of records, and standardized follow-up timing (± 2 weeks).

Outcomes

The primary outcome was the change in total behavioral score after six months. Secondary outcomes included frequency of individual symptoms and associations with demographic and clinical factors. Multivariate regression identified independent predictors of behavioral changes.

Statistical Analysis

Continuous variables were reported as mean $\pm$ SD; categorical variables as frequency and percentage. Paired t-tests assessed pre- vs. post-treatment differences, chi-square or Fisher's exact tests compared categorical variables, and one-way ANOVA compared EEG categories. Multiple linear regression was used to identify predictors, with assumptions verified.

Significance was set at $p < 0.05$.

Results

Baseline Characteristics of Participants

A total of 77 children with epilepsy completed both the baseline and six-month follow-up evaluations. The mean age of participants was 7.16 ± 3.24 years (range: 3–16 years), with 51.9% ($n = 40$) boys and 48.1% ($n = 37$) girls. The mean number of siblings per family was 2.06 ± 0.86 , and the mean age at seizure onset was 5.83 ± 3.42 years.

Regarding seizure type, 58.4% had generalized tonic-clonic seizures, 33.8% focal seizures, and 7.8% mixed or unclassified forms. Electroencephalographic (EEG) results were normal in 28.6%, showed focal abnormalities in 45.4%, and generalized abnormalities in 26.0% of participants. A family history of epilepsy was reported in 36.4% of the children, and 10.4% had a family history of hyperactivity. Perinatal complications (e.g., birth asphyxia or preterm delivery) were present in 14.3%, and 63.6% of children had been delivered by cesarean section. None had a history of metabolic or chromosomal disorders, head trauma, or major psychiatric illness prior to the study.

Behavioral Outcomes Before and After Levetiracetam (LEV) Therapy

Behavioral assessment based on DSM-5 criteria

showed a significant increase in behavioral symptoms following six months of Levetiracetam (LEV) therapy. The mean total behavioral score rose from 2.31 ± 0.94 before treatment to 3.74 ± 1.28 after treatment ($p < 0.001$, paired t-test).

Before LEV initiation, 10.4% of participants exhibited irritability, 6.5% impulsivity, and 5.2% restlessness. After six months, these rates increased to 27.3%, 16.9%, and 16.9%, respectively. Oppositional defiant traits increased from 3.9% to 10.4%, and anxiety or mood instability newly appeared in 9.1% of children. Sleep disturbances increased slightly (7.8% to 11.7%), though not significantly ($p = 0.322$).

In addition, hyperactivity symptoms (DSM-5 hyperactivity subscale) showed a significant rise after LEV therapy, with the mean score increasing from 2.44 ± 2.66 to 3.61 ± 3.81 ($p = 0.001$). Item-level analysis revealed that the proportion of “often” responses increased notably for most items, such as fidgeting or squirming (from 9.1% to 23.4%) and leaving seat when expected to remain seated (from 5.2% to 14.3%) (Table1).

Table 1: Frequency of Behavioral Symptoms Before and After 6 Months of Levetiracetam Therapy

Behavioral symptom	Before LEV, n (%)	After LEV, n (%)	p-value
Irritability	8 (10.4)	21 (27.3)	<0.001
Impulsivity	5 (6.5)	13 (16.9)	0.002
Restlessness	4 (5.2)	13 (16.9)	0.005
Anxiety / mood changes	0 (0)	7 (9.1)	0.01
Sleep disturbance	6 (7.8)	9 (11.7)	0.32
Oppositional defiant traits	3 (3.9)	8 (10.4)	0.04
Total behavioral score (mean $\pm$ SD)	2.31 ± 0.94	3.74 ± 1.28	<0.001

Paired t-test or Chi-square test applied as appropriate.

Overall, LEV administration was associated with a significant increase in hyperactive and impulsive behaviors consistent with DSM-5 criteria.

Association Between Demographic Variables and Behavioral Changes

Analysis of demographic and clinical factors revealed that younger children (<7 years) had significantly higher post-treatment behavioral scores compared with older participants (4.02 ± 1.31 vs. 3.48 ± 1.22 ; $p = 0.046$). Behavioral outcomes did not differ significantly by sex ($p = 0.384$) or seizure type ($p = 0.418$).

Children with a positive family history of epilepsy showed a greater, though not statistically significant, increase in behavioral scores (mean change = 1.69 ± 0.87 vs. 1.28 ± 0.65 ; $p = 0.061$). A significant association was found between EEG patterns and behavioral worsening: children with generalized EEG abnormalities exhibited the highest mean increase in behavioral score compared to those with focal or normal EEGs ($p = 0.037$).

No significant relationships were observed between behavioral changes and delivery mode ($p = 0.542$), perinatal complications ($p = 0.261$), or family history of hyperactivity ($p = 0.173$). Linear regression analysis A multivariate linear regression model was conducted to identify predictors of post-treatment behavioral scores. The dependent variable was the post-treatment behavioral score, while independent variables included baseline behavioral score, sex, history of metabolic or genetic disorders, seizure type, and age at seizure onset.

The analysis indicated that the baseline behavioral score was the strongest predictor of post-treatment behavioral outcome ($B = 0.677$, $p < 0.001$). Other predictors—including sex, seizure type, and age at onset—did not show significant associations.

Table 2: Linear Regression Analysis of Predictors of Post-Treatment Behavioral Score

Predictor	B	p-value
Baseline symptom score	0.67	< .001
Sex	-0.31	.53
History of metabolic disorder	-1.73	.28
History of genetic disorder	1.62	.09
Seizure type	-0.30	.63
Age at seizure onset	-0.12	
(Constant)	3.85	.37

EEG Findings and Clinical Associations

Children with generalized EEG abnormalities had a higher frequency of perinatal complications ($p = 0.03$) and head trauma ($p = 0.02$) compared with those with focal or normal EEG patterns. No significant associations were found with sex, developmental status, or family history of hyperactivity.

Adverse Effects and Drug Tolerability

Levetiracetam was generally well tolerated. None of the participants required discontinuation due to behavioral or other adverse effects. Mild fatigue was observed in 5.2%, loss of appetite in 3.9%, and somnolence in 2.6% of participants, all of which resolved spontaneously without dose modification.

Regarding seizure control, 61 of 77 children (79.2%) achieved at least a 50% reduction in seizure frequency, indicating favorable therapeutic efficacy of LEV despite the observed behavioral side effects.

Discussion

The present longitudinal study evaluated the behavioral effects of Levetiracetam (LEV) in children with epilepsy treated at Mofid Children's Hospital over a six-month period. The findings demonstrated a statistically significant increase in behavioral symptoms—particularly irritability, impulsivity, and restlessness—after initiation of LEV therapy. The frequency of these symptoms approximately doubled to tripled after treatment, and the total DSM-5 behavioral score increased from 2.31 to 3.74. These results reinforce the growing body of evidence indicating

that while LEV is highly effective in seizure control, it can induce or exacerbate behavioral and emotional disturbances in a subset of pediatric patients.

The pattern and magnitude of behavioral changes in this study are consistent with previous national and international findings. Tegköl et al. (2016) reported behavioral adverse effects in about 17% of children treated with LEV, with irritability being the most frequent manifestation (67%), followed by hyperactivity (8%) and sleepiness (6%) (17). Likewise, Cortés and Manterola (2020) found that 23.3% of children aged 4–15 years developed behavioral symptoms within four weeks of treatment, most commonly irritability and aggression (10). The rates of irritability (27.3%) and impulsivity (16.9%) observed in this study fall within the upper range of these reports. Similarly, Egunsola et al. (2018) found that behavioral side effects were about twice as common with LEV as with lamotrigine, although LEV was associated with fewer metabolic and hepatic adverse events (18).

Differences in reported prevalence among studies likely reflect variation in sample characteristics, follow-up duration, dosage, and assessment tools. The relatively high rate in our cohort may stem from the use of DSM-5 criteria, which capture a broader range of behavioral changes, as well as increased parental awareness due to structured follow-up.

Although the mechanisms underlying LEV-induced behavioral disturbances remain unclear, several hypotheses exist. LEV binds selectively to the synaptic vesicle protein 2A (SV2A), a key regulator of neurotransmitter release (19). While this mechanism explains its antiepileptic efficacy, it may also disrupt the delicate balance between excitatory glutamatergic and inhibitory GABAergic neurotransmission in brain regions governing emotion and impulse control (6). Animal studies suggest that LEV may reduce GABAergic inhibition and enhance glutamatergic signaling, producing neuronal hyperexcitability in the limbic and prefrontal regions—areas associated with behavioral and emotional regulation (6, 20). Children with developing brains may be especially vulnerable to these neurochemical alterations, predisposing them to irritability, impulsivity, or aggression. Another proposed mechanism involves modulation of monoaminergic systems, particularly serotonin and

dopamine, which could contribute to mood instability and individual variability in behavioral response (9, 21).

Age emerged as a significant determinant of behavioral response. Children younger than seven years were more likely to experience behavioral worsening. Prior studies have also demonstrated that behavioral side effects, especially hyperactivity and irritability, are more pronounced in younger children due to the immaturity of neural circuits responsible for emotional regulation and inhibitory control (22, 23). Although parental reporting bias may play a role, the consistent association and biological plausibility suggest that the relationship is genuine rather than subjective.

Our study also found a significant association between generalized EEG abnormalities and behavioral deterioration. Children with generalized epileptiform discharges had higher post-treatment behavioral scores compared with those with focal or normal EEG patterns. This may reflect the broader cortical and subcortical involvement in generalized epilepsy, predisposing these patients to greater behavioral vulnerability (17). Tegköl et al. (2016) similarly reported that patients with generalized spike-wave activity were nearly twice as likely to develop irritability and aggression (17), while Cortés and Manterola (2020) found no significant association, likely due to smaller sample size (10).

The predominant behavioral manifestations—irritability, impulsivity, and restlessness—closely resemble hyperactivity and ODD symptomatology. Previous literature has shown that LEV can provoke ADHD-like behaviors or worsen preexisting attention deficits, even in children without psychiatric history (23, 24). This overlap between epilepsy-related neurocognitive dysfunction and drug-induced behavioral effects complicates clinical interpretation (25, 26). Sleep disturbances in our cohort were mild and not statistically significant, diverging from other reports that noted increased insomnia or somnolence (10, 17). Such discrepancies could arise from differences in dose, timing, or concurrent medications.

Despite these behavioral effects, LEV achieved substantial seizure reduction in nearly 80% of participants, reaffirming its therapeutic value (27, 28). However, the emergence of behavioral symptoms underscores the need for ongoing behavioral monitoring during treatment. Clinicians should educate parents

about possible mood and activity changes, encouraging early reporting. Timely interventions—such as dose adjustment, temporary discontinuation, or behavioral therapy—can prevent escalation and improve adherence (24, 29, 30). Children under seven years and those with generalized EEG abnormalities represent higher-risk subgroups requiring closer monitoring and possibly lower initial doses. Collaboration with pediatric psychiatrists can assist in differentiating drug-induced changes from comorbid psychiatric disorders (30, 31).

Compared with older AEDs, LEV presents a unique behavioral profile. While valproate and phenobarbital are associated with sedation and cognitive slowing, LEV tends to cause activation-type symptoms such as irritability and hyperactivity (29, 32, 33). Egunsola et al. (2018) reported that behavioral adverse effects occurred roughly twice as often with LEV as with lamotrigine, although LEV showed fewer metabolic effects (18). Hence, treatment choice should balance seizure control efficacy against behavioral tolerability, especially in children with prior emotional or conduct issues, for whom alternatives like lamotrigine or oxcarbazepine may be preferred (34).

This study's strengths include its longitudinal within-subject design and use of standardized DSM-5-based behavioral assessments, enhancing reliability. Conducting the study in a tertiary pediatric center also ensured accurate diagnosis and consistent follow-up. Nonetheless, limitations include the lack of a control group, reliance on parental reporting, and absence of serum LEV level measurements, which precluded dose-response evaluation. The six-month duration may not capture long-term behavioral changes. Despite these constraints, the study fills a significant knowledge gap in Iranian pediatric epilepsy and aligns with global evidence.

Routine behavioral screening should be an integral part of pediatric epilepsy management, particularly during early LEV therapy. Multidisciplinary collaboration among neurologists, psychiatrists, and psychologists is recommended for children showing significant behavioral changes. Parental education should emphasize monitoring for emotional as well as seizure-related outcomes. Future studies should involve larger cohorts, pharmacogenetic analysis, and objective behavioral assessments.

Conclusion

This study demonstrated that Levetiracetam (LEV), while effective and well-tolerated for seizure control, can lead to notable behavioral adverse effects such as irritability, impulsivity, and restlessness in children with epilepsy. These effects were most pronounced in younger patients and those with generalized EEG abnormalities, suggesting increased neurobehavioral susceptibility in these groups. Although none of the patients discontinued therapy due to side effects, the findings emphasize the importance of regular behavioral monitoring, early recognition, and intervention through dose adjustment and family counseling. Overall, LEV remains a valuable therapeutic option, but clinicians should maintain vigilance toward its behavioral profile to balance seizure control with optimal quality of life in pediatric epilepsy care.

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Conflict of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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