Turkish Journal of Pediatric Disease

Original Article

Efficacy and safety of levetiracetam treatment in childhood epilepsy

Arife Toksöz[1], Serap Teber[2]

[1]Department of Pediatric Immunology and Allergy, Ankara Etlik City Hospital, Ankara, Türkiye
[2]Department Pediatric Neurology, Ankara University, Ankara, Türkiye

ABSTRACT

Objective: Levetiracetam (LEV) is a second-generation antiepileptic drug widely used in pediatric epilepsy due to its favorable pharmacokinetics, efficacy, and tolerability. This study aimed to evaluate the long-term efficacy and safety of LEV treatment in children with epilepsy.

Material and Methods: A retrospective review was conducted on pediatric patients diagnosed with epilepsy and treated with LEV at a tertiary pediatric neurology center. Treatment efficacy was assessed based on seizure frequency reduction of more than 50% or complete seizure freedom. The occurrence and types of adverse effects were also analyzed. Statistical analyses included chi-square tests, independent t-tests, and logistic regression models.

Results: A total of 101 patients were included in the study. LEV was initiated as the first antiepileptic drug in 9.9% of patients. By the end of the follow-up, 34.7% remained on LEV treatment, and 11.9% discontinued LEV. LEV was effective in 72.3% of patients, with 38.0% achieving complete seizure freedom. The drug was significantly more effective in patients older than four years and those with a lower pre-treatment seizure frequency. The mean LEV dose was 24.8 mg/kg/day in the effective group and 33.8 mg/kg/day in the ineffective group. Adverse effects were observed in 45.5% of patients, with the most common being drowsiness, irritability, and fatigue. Patients with a prior history of adverse reactions to other antiepileptic drugs had a significantly higher likelihood of developing side effects with LEV.

Conclusion: Levetiracetam (LEV) is an effective and well-tolerated treatment option for childhood epilepsy, with high efficacy rates and a manageable safety profile. Older children, those receiving lower doses, and those with a lower pre-treatment seizure burden demonstrated better treatment outcomes. Careful monitoring is necessary for patients with a history of adverse reactions to other anti-epileptic drugs.

Keywords: Antiepileptic drugs, children, epilepsy, levetiracetam, seizure control, safety, tolerability

INTRODUCTION

Epilepsy is defined as the occurrence of two or more unprovoked seizures at least 24 hours apart (1). As the second most common neurological disorder after headaches, it is a chronic disease affecting 0.5–1% of children under 16 years of age (2,3). The primary goal of antiepileptic treatment is to achieve seizure freedom without adverse effects.

Levetiracetam [(S)-α-ethyl-2-oxo-1-pyrrolidineacetamide] is a water-soluble pyrrolidine derivative and a new-generation antiepileptic drug introduced in 2000 (4). The U.S. Food and Drug Administration (FDA) initially approved LEV in 1999 as an adjunctive therapy for drug-resistant partial epilepsy in adults, extending its approval in 2005 to include individuals over four years of age (5,6). Currently, LEV is indicated as adjunctive therapy for myoclonic seizures in adults and adolescents (≥12 years) with juvenile myoclonic epilepsy, partial seizures in adults and infants (≥1 month) with epilepsy, and primary generalized tonic-clonic seizures in adults and children (≥5 years) with idiopathic generalized epilepsy (7).

This study aimed to evaluate the long-term efficacy and safety of LEV treatment in children with epilepsy.

Correspondence Address:
Arife TOKSÖZ
e-mail: arifetoksoz@gmail.com

Received : 23.02.2025
Accepted : 08.07.2025
DOI: 10.12956/TJPD.2025.1221

MATERIALS and METHODS

This retrospective chart review included 101 patients who were diagnosed with epilepsy and started on levetiracetam (LEV) treatment in the Pediatric Neurology Clinic of Ankara Child Health and Diseases Hematology-Oncology Training and Research Hospital between 01.01.2010 and 30.12.2011.

Epilepsy was defined as two or more unprovoked seizures occurring at least 24 hours apart. Treatment efficacy was determined based on a reduction of over 50% in seizure frequency or complete seizure freedom with LEV.

Statistical Analyses

Data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including mean, standard deviation, frequency, and percentage, were used to summarize the data. Pearson's chi-square test and the independent t test were used to compare groups. All statistical analyses were two-tailed, with a significance level set at 0,050 and a 95% confidence interval.

RESULTS

A total of 101 patients were included in the study, of whom 41 (40.6%) were female and 60 (59.4%) were male. The mean age of the participants was 12.6 ± 4.7 years (range, 1.5–23 years) (Table I).. LEV was initiated as the first antiepileptic drug in 10 (9.9%) of the 101 patients. By the end of the treatment period, 35 (34.7%) patients were on LEV monotherapy, while LEV was discontinued in 12 (11.9%) patients. Table II presents the clinical characteristics associated with LEV treatment, observed adverse effects, and seizure outcomes at final follow-up.

Levetiracetam was found to be effective in 72.3% (73/101) of patients. No statistically significant differences were observed between LEV efficacy and patients' sex, age, or age at diagnosis. In patients with effective LEV treatment (n=73), the mean age at initiation was 11.25±3.94 years, which was significantly higher than the mean age of 8.86±5.43 years observed in those with an ineffective response (n=28) (p=0.040). The mean LEV dose was 24.8±9.6 mg/kg/day in the effective group, whereas it was 33.8±9.05 mg/kg/day in the ineffective group, with a statistically significant difference (p=0.001). Details regarding LEV treatment efficacy are presented in Table III.

LEV treatment was discontinued in 12 out of our 101 patients. Among these, 5 (41.7%) discontinued due to lack of efficacy, 4 (33.3%) due to side effects, and 3 (25%) due to increased seizure frequency. The mean duration of LEV use in these patients was 9.5±8.2 months.

Side effects were observed in 46 patients (45.5%), including drowsiness, irritability, fatigue, aggression, dizziness, insomnia, headache, vomiting, and loss of appetite. Among all patients, 19 (18.8%) had previously experienced side effects from another antiepileptic drug (AED) and 13 of these 19 (68.4%) also developed side effects with LEV. Among these 19 patients, adverse effects were observed in 6 patients (31.6%) with valproic acid, 6 patients (31.6%) with carbamazepine, 3 patients (15.8%) with lamotrigine, 2 patients (10.5%) with clonazepam, 1 patient (5.3%) with oxcarbazepine, and 1 patient (5.3%) with primidone. Table III presents the factors influencing the

Table I: Demographic, clinical, and laboratory characteristics, imaging, and electroencephalographic findings of the patients

Gender*	
Female	41 (40.6)
Male	60 (59.4)
Age (years)†	12.6±4.7 (1.5-23)
Age at epilepsy diagnosis (years) †	5.5±4.5 (0.1-17)
Seizure Classification*	
Generalized Seizure	77 (76.2)
Focal Seizure	24 (23.8)
Mental and motor developmental delay	48 (47.5)
History of febrile convulsions	19 (18.8)
History of past illness	72 (71.3)
Use of other medications	35 (34.7)
History of hospitalization	65 (64.4)
Academic Performance*	
Regular education	47 (46.5)
Special education	46 (45.5)
Not attending school	8 (8)
Family history of epilepsy	33 (32.7)
Family history of neurological disorders	38 (37.6)
Pathological findings on systemic examination	4 (4)
Neurological Examination Findings*	
Mental retardation	57 (56.4)
Motor retardation	43 (42.6)
Microcephaly	29 (28.7)
Syndromic appearance	13 (12.9)
Abnormal EEG *	75 (74.2)
Abnormal MRI*	72 (71.2)
Etiology*	
Unknown	46 (45.5)
Hypoxic-ischemic encephalopathy	13 (12.9)
Structural CNS abnormalities	8 (7.9)
Specific epileptic syndromes	7 (6.9)
Thromboembolism – Infarct	6 (5.9)
CNS infections	5 (5)
Metabolic disorders	5 (5)
Chromosomal anomalies	3 (3)
CNS tumor	3 (3)
Intracranial hemorrhage	3 (3)
Intrauterine infection	1 (1)
Trauma	1 (1)

:** *n (%),* **†:** *mean±SD (min-max),* ***EEG: *Electroencephalography,* ***MRI:*** *Magnetic Resonance Imaging,* ***CNS:*** *Central Nervous System*

Table II: Clinical features related to lev treatment, adverse effects, and follow-up seizure outcomes

Seizure Frequency Before LEV Treatment*	
1 or fewer seizures per year	4 (4)
Less than 1 seizure per 6 months	11 (10.9)
1 or fewer seizures per month	36 (35.6)
More than 1 seizure per month	50 (49.5)
Seizure Duration Before LEV Treatment*	
<1 minute	29 (28.7)
1–5 minutes	34 (33.7)
5–30 minutes	35 (34.7)
Status epilepticus	3 (3)
LEV Treatment Details†	
Age at LEV initiation (years)	10.5±4.5 (0.6-20.5)
Order of LEV usage	3.7±2.1 (1-10)
Initial LEV dose (mg/kg/day)	10.8±4.2 (5-25)
Final LEV dose (mg/kg/day)	27.3 ±10.2
Duration of LEV treatment (months)	21.7±15.08
Adverse Effects of LEV Treatment*	
Any adverse effect observed	46 (45.5)
No adverse effect	55 (54.5)
Types of Adverse Effects Observed*	
Drowsiness / Excessive sleep	14 (13.9)
Irritability	13 (12.9)
Fatigue	9 (8.9)
Aggressiveness*	6 (5.9)
Dizziness	5 (5)
Insomnia	4 (4)
Reduction in aggressiveness	4 (4)
Headache	3 (3)
Vomiting	3 (3)
Loss of appetite	2 (2)
Other	11 (11)
Seizure Frequency at Final Follow-up After LEV Treatment*	
Seizure-free	39 (38)
>50% reduction in seizure frequency	34 (34)
<50% reduction in seizure frequency	8 (8)
No change in seizure frequency	12 (12)
Increased seizure frequency	8 (8)

:** *n (%),* **†:** *mean±SD (min-max),* ***LEV: *Levetiracetam*

development of side effects in patients who were initiated on LEV treatment.

DISCUSSION

Levetiracetam is considered a favorable option for the treatment of childhood epilepsy due to its efficacy and tolerability. Recent studies report LEV efficacy rates ranging from 44% to 94% (8-10). A retrospective study conducted by Tekgül H. et al. (11) in Türkiye, involving 351 pediatric epilepsy patients aged 6 months to 18 years, demonstrated that LEV was effective in 65% of cases following a 12-month follow-up period. Similarly, our findings indicate that LEV was effective in 72.3% of patients. The variability in reported LEV efficacy may be attributed to the significant heterogeneity of study populations.

Initially approved for drug-resistant focal epilepsy in adults, LEV was suggested to be more effective in partial epilepsy. However, multiple studies have found no significant difference in efficacy between generalized and partial epilepsy (12-18). In the present analysis, when end-of-treatment efficacy was evaluated based on seizure type, LEV was effective in 55 of 77 (71.4%) patients with generalized epilepsy and in 18 of 24 (75%) patients with partial epilepsy. No statistically significant difference in efficacy was observed between patients with generalized and partial epilepsy.

A multicenter, double-blind, randomized study comparing patients receiving 4000 mg/day and 2000 mg/day of LEV to those receiving a placebo found LEV to be more effective at a dose of 2000 mg/day, while no significant difference was observed between the 4000 mg/day group and the placebo group (19). In contrast, some studies suggest that higher LEV doses are more effective, whereas others report no significant relationship between LEV dose and efficacy (16,20,21). Additionally, a review by Sourbron et al. (22) highlighted that in children aged 2 months to 12 years, LEV clearance is 30-70% higher compared to adults, indicating that higher LEV doses may be required in this age group. Consistent with these findings, our results demonstrated that the mean LEV dose was significantly lower in patients for whom LEV was effective than in those for whom it was ineffective (p=0.001).

Although studies on LEV efficacy in younger age groups are limited, a retrospective analysis of 122 epilepsy patients under four years old reported a reduction in seizure frequency in 57% of patients, primarily those with partial epilepsy requiring lower LEV doses. Hu et al. (24) studied 120 patients aged four months to four years with refractory epilepsy, finding that after a mean follow-up of 13 months, 38.4% achieved a ≥50% seizure reduction, and 12.5% became seizure-free. Kanmaz et al. (25) examined 67 neonates treated with LEV, reporting that after one year, 76% achieved seizure freedom with LEV monotherapy, and 63.8% showed positive neurodevelopmental outcomes. Arzimanoglou et al. (26) found a 71.8% LEV efficacy rate in 100 infants aged 1-11 months, while Zhao et al. (27) reported a 41% seizure-free rate over 12 months in 78 patients (aged 2-24 months) receiving LEV monotherapy (23-25). In the present study, LEV was effective in 28.6% of patients who started treatment at ≤4 years and in 75.5% of those who started at >4 years (p=0.017). The small sample size for patients under four years old (7/101) may have limited our evaluation, underscoring the need for larger cohorts in future prospective studies.

Studies investigating the relationship between seizure frequency before LEV treatment and LEV efficacy have shown that patients experiencing two or more seizures per month prior to LEV initiation had a poorer response to treatment (23). In this analysis, LEV was significantly more effective in patients who had one or fewer seizures per month before treatment (p =0.012).

Although LEV is generally well tolerated, literature reviews indicate that side effects occur in 7% to 55% of patients (12-

Table III: Efficacy data of LEV in patients initiated on treatment and factors influencing adverse effects

Group	n	Effective Response to LEV Treatment		Patients experiencing adverse effects	
		n (%)	p*	n (%)	p*
Generalized Epilepsy Focal Epilepsy	72 24	55 (71.4) 18 (75)	0.936	-	-
LEV Initiation Age ≤ 4 years LEV Initiation Age > 4 years	7 94	2 (28.6) 71 (75.5)	0.017	2 (28.6) 44 (46.8)	0.450
Pre-Treatment Seizure Frequency ≤ 1 per month Pre-Treatment Seizure Frequency > 1 per month	51 50	43 (84.3) 30 (60)	0.012	22 (43.1) 24 (48)	0.624
LEV Initiated as Adjunctive Therapy LEV Initiated as First-Line Therapy	91 10	63 (69.2) 10 (100)	0.058	41 (45.1) 5 (50)	0.998
Initial Dose <10 mg/kg/day Initial Dose ≥10 mg/kg/day	60 41	44 (73.3) 29 (70.7)	0.952	27 (45) 19 (46.3)	0.894
Final Dose <40 mg/kg/day Final Dose ≥40 mg/kg/day	89 12	65 (73) 8 (66.7)	0.733	40 (44.9) 6 (50)	0.983
LEV Treatment Order ≤ 4 LEV Treatment Order ≥ 5	76 25	56 (73.7) 17 (68.0)	0.769	34 (44.7) 12 (48)	0.958
LEV Treatment Duration ≤ 12 months LEV Treatment Duration > 12 months	37 64	-	-	16 (43.2) 30 (46.9)	0.724
Normal Neurological Examination Abnormal Neurological Examination	51 50	41 (80.4) 32 (62)	0.106	-	-
Normal EEG Abnormal EEG	26 75	22 (84.6) 51 (68)	0.113	-	-
Normal MRI Abnormal MRI	29 72	23 (79.3) 50 (69.4)	0.449	-	-

***:** *Pearson Chi-Square test,* ***EEG:** Electroencephalography,* ***MRI:** Magnetic Resonance Imaging,* ***LEV:** Levetiracetam*

18). In the current study, at least one side effect was observed in 46 patients (45.5%). Additionally, 19 patients (18.8%) had previously experienced side effects from another AED before LEV initiation. Among these, 13 (68.4%) also developed side effects with LEV (p=0.049), suggesting a predisposition to adverse reactions. This finding highlights the importance of reviewing patients' prior AED histories before initiating LEV treatment.

CONCLUSION

This study demonstrated that levetiracetam is an effective, well-tolerated, and safe treatment for childhood epilepsy. Although it may cause side effects or an increase in seizures, these effects were generally mild and transient, not necessitating treatment discontinuation in most patients. Efficacy was higher in children over four years of age, those receiving lower doses, and those with less frequent seizures before treatment. The risk of side effects was found to be higher in patients who had previously experienced side effects from another AED.

Additional information

Presented at the 44th Pediatrics Days, 23rd Pediatric Nursing Days, April 17-20, 2022, Online Congress

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by The study was approved by the Education Planning and Coordination Committee of the Ankara Children's Health and Diseases Hematology Oncology Education and Research Hospital. (06.02.2012, reference number: 95).

Contribution of the authors

Study conception and design: ***AT, ST***; data collection: ***AT***; analysis and interpretation of results: ***AT, ST***; draft manuscript preparation: ***AT, ST***. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. World Health Organization (WHO). Epilepsy. Available online: https://www.who.int/news-room/fact-sheets/detail/epilepsy (accessed on 6 October 2021).
2. Fine A, Wirrell EC. Seizures in Children. Pediatr Rev. 2020 Jul;41(7):321-347. doi: 10.1542/pir.2019-0134
3. Biset G, Abebaw N, Gebeyehu NA, Estifanos N, Birrie E, Tegegne KD. Prevalence, incidence, and trends of epilepsy among children and adolescents in Africa: a systematic review and meta-analysis. BMC Public Health. 2024;24(1):771. doi: 10.1186/s12889-024-18236-z.

4. Contreras-García IJ, Cárdenas-Rodríguez N, Romo-Mancillas A, Bandala C, Zamudio SR, Gómez-Manzo S et al. Levetiracetam Mechanisms of Action: From Molecules to Systems. Pharmaceuticals (Basel). 2022;15(4):475. doi: 10.3390/ph15040475.
5. Agrawal A, Banergee A. A Review on Pharmacokinetics of Levetiracetam in Neonates. Curr Drug Metab. 2017;18(8):727-734. doi: 10.2174/1389200218666170607100054.
6. Wu PP, Cao BR, Tian FY, Gao ZB. Development of SV2A Ligands for Epilepsy Treatment: A Review of Levetiracetam, Brivaracetam, and Padsevonil. Neurosci Bull. 2024;40(5):594-608. doi: 10.1007/s12264-023-01138-2.
7. Kumar A, Maini K, Kadian R. Levetiracetam. 2023 Dec 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.
8. Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L et al. Neurological Emergencies Treatment Trials; Pediatric Emergency Care Applied Research Network investigators. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet. 2020;395(10231):1217-24. doi: 10.1016/S0140-6736(20)30611-5.
9. Besli GE, Yuksel Karatoprak E, Yilmaz S. Efficacy and safety profile of intravenous levetiracetam versus phenytoin in convulsive status epilepticus and acute repetitive seizures in children. Epilepsy Behav. 2020;111:107289. doi: 10.1016/j.yebeh.2020.107289.
10. Yi ZM, Zhong XL, Wang ML, Zhang Y, Zhai SD. Efficacy, Safety, and Economics of Intravenous Levetiracetam for Status Epilepticus: A Systematic Review and Meta-Analysis. Front Pharmacol. 2020;11:751. doi: 10.3389/fphar.2020.00751.
11. Tekgül H, Gencpinar P, Çavuşoğlu D, Dündar NO. The efficacy, tolerability and safety of levetiracetam therapy in a pediatric population. Seizure. 2016;36:16-21. doi: 10.1016/j.seizure.2016.01.017.
12. Mazur RD, Wang Ba Q, Kato Bs K, Buchsbaum Bs R, Bonito Bs J, Choi H et al. Effectiveness of Levetiracetam Monotherapy in Pediatric Patients With Epilepsy. J Child Neurol. 2019;34(10):593-597. doi: 10.1177/0883073819846804.
13. Nevitt SJ, Sudell M, Cividini S, Marson AG, Tudur Smith C. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2022;4(4):CD011412. doi: 10.1002/14651858.CD011412.pub4.
14. Yıldırım M, Bektaş Ö, Akıncı Göktaş Ö, Yüksel MF, Şahin S, Tıraş Teber S. Levetiracetam monotherapy in children with epilepsy: Experience from a tertiary pediatric neurology center. Epilepsy Behav. 2021;116:107745. doi: 10.1016/j.yebeh.2020.107745.
15. Razieh R, Shafiei A, Dehghani Firouzabadi F, Fathi A. Evaluation of the efficacy and tolerability of levetiracetam as add-on therapy in intractable epilepsy of children. Iran J Child Neurol. 2022 Spring;16(2):77-84. doi: 10.22037/ijcn.v15i4.29028.
16. Sheinberg R, Heyman E, Dagan Z, Youngster I, Kohn E, Gandelman-Marton R et al. M. Correlation between efficacy of levetiracetam and serum levels among children with refractory epilepsy. Pediatr Neurol. 2015;52(6):624-8. doi: 10.1016/j.pediatrneurol.2015.01.012.
17. Campos MSA, Ayres LR, Morelo MRS, Carizio FAM, Pereira LRL. Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analyses. Int J Clin Pharm. 2018 Jun;40(3):589-598. doi: 10.1007/s11096-018-0641-9.
18. Abou-Khalil BW. Update on Antiepileptic Drugs 2019. Continuum (Minneap Minn). 2019;25(2):508-536. doi: 10.1212/CON.0000000000000715.
19. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. Seizure. 2000;9(2):80-7. doi: 10.1053/seiz.2000.0380.
20. Mateo-Carrasco H, Serrano-Castro PJ, Molina-Cuadrado E, Goodwin M, Nguyen TV, Kotecha PN. Role of high-dose levetiracetam as add-on therapy for intractable epilepsy: case report and brief review of the literature. Int J Clin Pharm. 2015;37(4):559-62. doi: 10.1007/s11096-015-0105-4.
21. Iwasaki T, Toki T, Nonoda Y, Ishii M. The efficacy of levetiracetam for focal seizures and its blood levels in children. Brain Dev. 2015;37(8):773-9. doi: 10.1016/j.braindev.2014.11.008.
22. Sourbron J, Chan H, Wammes-van der Heijden EA, Klarenbeek P, Wijnen BFM, de Haan GJ et al. Review on the relevance of therapeutic drug monitoring of levetiracetam. Seizure. 2018;62:131-135. doi: 10.1016/j.seizure.2018.09.004.
23. Perry MS, Benatar M. Efficacy and tolerability of levetiracetam in children younger than 4 years: a retrospective review. Epilepsia. 2007;48(6):1123-7. doi: 10.1111/j.1528-1167.2007.01003.x.
24. Hu Y, Liao JX, Chen L, Huang TS, Li B. Efficacy and safety of adjunctive levetiracetam in children younger than 4 years with refractory epilepsy. Zhongguo Dang Dai Er Ke Za Zhi. 2010;12(4):256-8.
25. Kanmaz S, Altun Köroğlu Ö, Terek D, Serin HM, Simsek E, Dokurel Cetin İ et al. Efficacy of levetiracetam as first-line therapy for neonatal clinical seizures and neurodevelopmental outcome at 12 months of age. Acta Neurol Belg. 2021;121(6):1495-1503. doi: 10.1007/s13760-020-01366-7.
26. Arzimanoglou A, Lösch C, Garate P, Bentz J. Safety of levetiracetam among infants younger than 12 months--Results from a European multicenter observational study. Eur J Paediatr Neurol. 2016;20(3):368-75. doi: 10.1016/j.ejpn.2016.01.006.
27. Zhao B, Liao S, Zhong X, Luo Y, Hong S, Cheng M, et al. Effectiveness and Safety of Oxcarbazepine vs. Levetiracetam as Monotherapy for Infantile Focal Epilepsy: A Longitudinal Cohort Study. Front Neurol. 2022;13:909191. doi: 10.3389/fneur.2022.909191.