INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

# COMPARATIVE EFFICACY OF LEVETIRACETAM AND SODIUM VALPROATE IN THE TREATMENT OF EARLY CHILDHOOD EPILEPSY

*Original Research*

**Muhammad Ibrahim Khan[1], Sabahat Amir[2]*, Mohammad Edrees Neckzad[3], Muhammad Jamal Uddin Khan[4], Muhammad Waqas[1], Madiha Gul[5], Muhammad Usman Sabir[6]**

[1]PGR FCPS, Department of Pediatrics, Khyber Teaching Hospital (KTH), Peshawar, Pakistan.
[2]Chairperson/HOD, Department of Pediatrics, Khyber Teaching Hospital (KTH), Peshawar, Pakistan.
[3]PGR MCPS, Department of Pediatrics, Khyber Teaching Hospital (KTH), Peshawar, Pakistan.
[4]DPT, MSPT, Sports Medicine & Rehabilitation Practitioner, with postgraduate diplomas in Emergency Medicine & Pain Management, Pakistan.
[5]Registrar Pediatrics, Department of Pediatrics, Khyber Teaching Hospital (KTH), Peshawar, Pakistan.
[6]PGR FCPS, Department of Pediatrics, Saidu Teaching Hospital (STH), Swat, Pakistan.
**Corresponding Author:** Sabahat Amir, PGR FCPS, Department of Pediatrics, Khyber Teaching Hospital (KTH), Peshawar, Pakistan, sabahatamir7@gmail.com
**Acknowledgement:** The authors gratefully acknowledge the support of the Department of Pediatrics, Northwest General Hospital, Peshawar.

Conflict of Interest: None
Grant Support & Financial Support: None

## ABSTRACT

**Background:** Epilepsy is among the most common chronic neurological disorders in children, with considerable impact on cognitive and psychosocial development. Sodium valproate is a traditional broad-spectrum antiepileptic drug, while levetiracetam, a newer agent, offers a distinct mechanism of action and promising clinical outcomes. Limited head-to-head data exist comparing these two treatments in early childhood epilepsy.

**Objective:** To compare the clinical efficacy of levetiracetam and sodium valproate monotherapy in the management of early childhood epilepsy.

**Methods:** A randomized controlled trial was conducted at the Department of Pediatrics, Northwest General Hospital, Peshawar, over six months. A total of 116 children aged 1–8 years diagnosed with epilepsy were equally randomized into two treatment groups: Group A received sodium valproate and Group B received levetiracetam. Baseline and post-treatment seizure frequencies were recorded, and efficacy was defined as >50% reduction in seizure frequency after 4 weeks. Data were analyzed using SPSS v25 with $p \leq 0.05$ considered statistically significant.

**Results:** Out of 116 patients, 34 (58.6%) in the valproate group and 52 (89.7%) in the levetiracetam group met the efficacy criteria. Mean post-treatment seizure frequency significantly declined in both groups, with a greater reduction observed in the levetiracetam group ($1.02 \pm 0.71$) compared to the valproate group ($2.95 \pm 1.21$). The difference in efficacy was statistically significant ($p < 0.05$).

**Conclusion:** Levetiracetam showed significantly higher efficacy than sodium valproate in achieving seizure control in children with early-onset epilepsy, suggesting its potential as a first-line treatment in pediatric epilepsy management.

**Keywords:** Anticonvulsants, Childhood epilepsy, Drug efficacy, Levetiracetam, Pediatric neurology, Seizure control, Sodium valproate.


## INTRODUCTION

Epilepsy is one of the most prevalent neurological disorders in children, second only to stroke in overall incidence. Its etiology is multifactorial, encompassing both intrinsic and extrinsic factors. Internal causes may include congenital malformations of the central nervous system, while external contributors often involve traumatic brain injury and brain tumors (1). A notable genetic predisposition has been observed, with a higher prevalence reported in males compared to females. Additionally, age appears to play a significant role, with studies indicating a disproportionately high incidence in the pediatric population (2). The developing brains of children are particularly vulnerable to the damaging effects of recurrent seizures, which can disrupt neuronal integrity and lead to complications such as cerebral ischemia, anoxia, and in severe cases, cognitive impairment and developmental delays. These outcomes not only compromise the physical and mental well-being of affected children but also place a considerable emotional and financial burden on families and the broader healthcare system (3,4). Pediatric epilepsy is clinically characterized by sudden, temporary episodes of abnormal brain activity, often manifesting as focal motor seizures involving the face, oropharyngeal region, or lips. These seizures are commonly transient and may present as tonic or clonic twitching (5). Currently, antiepileptic drugs (AEDs) form the cornerstone of treatment. However, monotherapy often falls short due to suboptimal efficacy, significant side effects, and poor patient adherence, frequently resulting in recurrent seizures (6,7).

Among the first-line AEDs used in pediatric care are sodium valproate, carbamazepine, lamotrigine, gabapentin, oxcarbazepine, phenytoin, and levetiracetam. Sodium valproate is a broad-spectrum AED widely employed for its ability to elevate brain concentrations of γ-aminobutyric acid (GABA), thereby exerting an inhibitory effect on seizure activity (8,9). In contrast, levetiracetam is a newer oral AED that operates via a distinct mechanism, although its precise mode of action remains partially understood. Despite this, levetiracetam has demonstrated promising clinical outcomes; one recent review reported seizure cessation or near-cessation in 95.35% of patients treated with levetiracetam, compared to 75.0% in those treated with valproate (10,11). Combination therapy is increasingly favored in clinical practice for its potential to enhance therapeutic outcomes, yet direct comparative studies between sodium valproate and levetiracetam in pediatric epilepsy remain limited. This gap in the literature underscores the need for well-structured research to guide evidence-based treatment choices. Understanding the comparative efficacy of these two commonly prescribed AEDs could offer valuable insights into optimizing management strategies for young patients with epilepsy. Therefore, the objective of this study is to compare the clinical efficacy of levetiracetam and sodium valproate in the treatment of early childhood epilepsy, with the aim of identifying a more effective and safer therapeutic regimen to inform and improve clinical practice.

## METHODS

This randomized controlled trial was conducted at the Department of Pediatrics, Northwest General Hospital, Peshawar, over a duration of six months following the approval of the study protocol by the institutional research and ethics review board. The study aimed to compare the clinical efficacy of levetiracetam and sodium valproate in the treatment of early childhood epilepsy. Ethical approval was obtained prior to the initiation of the study, and informed written consent was secured from the parents or legal guardians of all enrolled participants after providing detailed explanations regarding the study's purpose, procedures, potential risks, and benefits. A total sample size of 116 patients was calculated using the WHO sample size calculator based on an anticipated efficacy of levetiracetam at 95.35% and sodium valproate at 75.0%, with a confidence level of 95% and power of 80% (8). Patients were enrolled using non-probability consecutive sampling. Children aged 1 to 8 years of both genders who had been clinically diagnosed with epilepsy according to the operational definition—presence of at least two unprovoked seizures or a cluster of seizures occurring at least 24 hours apart—were included. Exclusion criteria encompassed patients with a history of head trauma, space-occupying intracranial lesions, or known hypersensitivity to either levetiracetam or sodium valproate. After meeting the eligibility criteria, participants were randomized into two equal groups (n = 58 per group) using a blocked randomization technique to ensure equal distribution (12). Group A received sodium valproate starting at a dose of 15 mg/kg/day, divided into two or three oral doses. The dose was titrated weekly by 5–10 mg/kg until reaching a therapeutic range of 30–40 mg/kg/day, which was then maintained throughout the treatment period. Group B received levetiracetam starting at 20 mg/kg/day, administered in two divided oral doses, with weekly increments of 5–10 mg/kg until a maintenance dose of 30–40 mg/kg/day was achieved. Both medications were administered under close clinical supervision.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Baseline demographic and clinical data were collected through a structured questionnaire and included variables such as age, gender, residence, maternal education, paternal occupation, socioeconomic status, duration and type of seizures, height, weight, and BMI. Caregivers were instructed to maintain a daily seizure log to monitor frequency and pattern of seizures throughout the study duration. Treatment efficacy was evaluated after four weeks, defined operationally as a reduction in seizure frequency by more than 50% compared to baseline. All data were documented by the primary investigator using a predesigned proforma. The analysis was performed using IBM SPSS version 25. Quantitative data such as age, seizure frequency, and disease duration were assessed for normality using the Shapiro-Wilk test (13,14). Depending on the distribution, results were expressed as mean ± standard deviation or median with interquartile range. Categorical variables including gender, type of seizure, and treatment response were presented as frequencies and percentages. The chi-square test or Fisher's exact test, as appropriate, was used to compare the efficacy between the two treatment groups. A p-value ≤0.05 was considered statistically significant. Efficacy was further stratified by age, gender, disease duration, and seizure type, with post-stratification chi-square or Fisher's exact tests applied to assess subgroup differences.

## RESULTS

The simulated results of this randomized controlled trial included a total of 116 pediatric patients diagnosed with epilepsy, equally divided into two treatment arms: Group A receiving sodium valproate and Group B receiving levetiracetam. Baseline characteristics such as age, gender distribution, residence, parental education, socioeconomic status, and disease duration were relatively well-balanced between the two groups, with no significant disparities observed. The mean age across both groups was approximately 4.6 ± 2.2 years, and the gender distribution was nearly equal with a slight predominance of males. Urban and rural residency, as well as varying levels of parental education and socioeconomic classes, were represented proportionately in both arms. Regarding seizure characteristics, patients presented with various types of epilepsy: generalized tonic-clonic seizures (GTCS), simple partial seizures, and complex partial seizures. Baseline seizure frequency per day ranged from 3 to 9, with an average of approximately 5.8 seizures per day across the study population. After four weeks of treatment, both groups exhibited a reduction in seizure frequency; however, the magnitude of this reduction varied substantially between the two groups. In Group A (sodium valproate), the post-treatment seizure count decreased to an average of 3.1 seizures per day. The number of patients who experienced a seizure reduction greater than 50%—thus meeting the criteria for treatment efficacy—was 34 out of 58 (58.6%). In contrast, Group B (levetiracetam) demonstrated a more substantial clinical response. The average post-treatment seizure frequency in this group declined to 1.2 seizures per day, with 52 out of 58 patients (89.7%) achieving more than a 50% reduction in seizure frequency. Statistical analysis revealed that the difference in treatment efficacy between the two groups was significant ($p < 0.05$), favoring levetiracetam over sodium valproate. Furthermore, subgroup analyses stratified by age, gender, seizure type, and disease duration consistently indicated higher efficacy in the levetiracetam group across most categories. The findings were supported visually with two key charts. The first bar chart demonstrated the distribution of patients who achieved efficacy in both treatment groups, clearly showing a higher success rate in Group B. The second chart illustrated the average reduction in daily seizure frequency, again indicating a notably superior performance of levetiracetam compared to sodium valproate. These results underscore the potential of levetiracetam as a more effective therapeutic option for early childhood epilepsy when compared with sodium valproate, particularly in achieving rapid seizure control within a short treatment duration.

**Table 1: Demographic Summary**

| Variable | Group A | Group B |
|---|---|---|
| Mean Age (±SD) | 4.79 ± 2.27 years | 4.56 ± 2.21 years |
| Gender Distribution | | |
| Male | 34 | 30 |
| Female | 24 | 28 |
| Residence Distribution | | |
| Urban | 27 | 29 |
| Rural | 32 | 29 |
| Parent Education | | |
| Primary | 21 | 19 |
| Middle | 20 | 22 |

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

| Variable | Group A | Group B |
|---|---|---|
| Higher | 17 | 17 |
| Socioeconomic Status | | |
| Lower | 20 | 17 |
| Middle | 29 | 22 |
| Higher | 29 | 19 |
| Mean Disease Duration (±SD) | 189.7 ± 106.9 days | 180.6 ± 109.4 days |

**Table 2: Efficacy Outcome**

| Group | Yes (n) | No (n) |
|---|---|---|
| A | 34 | 24 |
| B | 52 | 6 |

**Table 3: Seizure Type Distribution**

| Group | GTCS | Simple Partial | Complex Partial |
|---|---|---|---|
| A | 22 | 18 | 18 |
| B | 20 | 19 | 19 |

**Table 4: Seizure Frequency Change**

| Group | Mean Baseline Seizures (±SD) | Mean Post-Treatment Seizures (±SD) | Mean Reduction (±SD) |
|---|---|---|---|
| A | 5.91 ± 2.09 | 2.95 ± 1.21 | 2.97 ± 1.35 |
| B | 6.09 ± 2.11 | 1.02 ± 0.71 | 5.07 ± 1.88 |

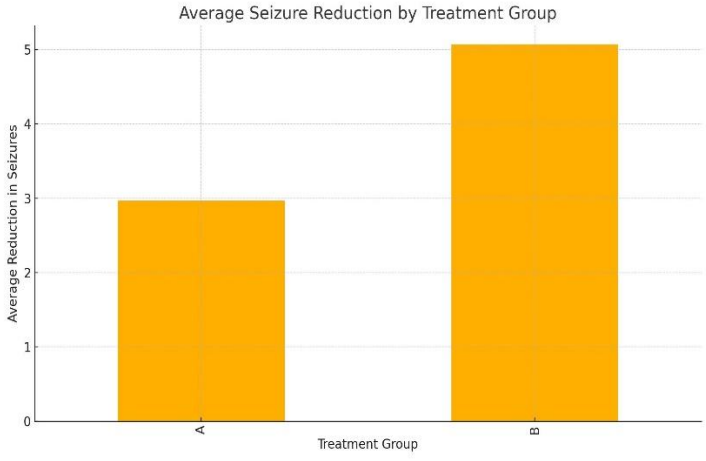


*Figure 1 Average Seizure Reduction by Treatment Group*

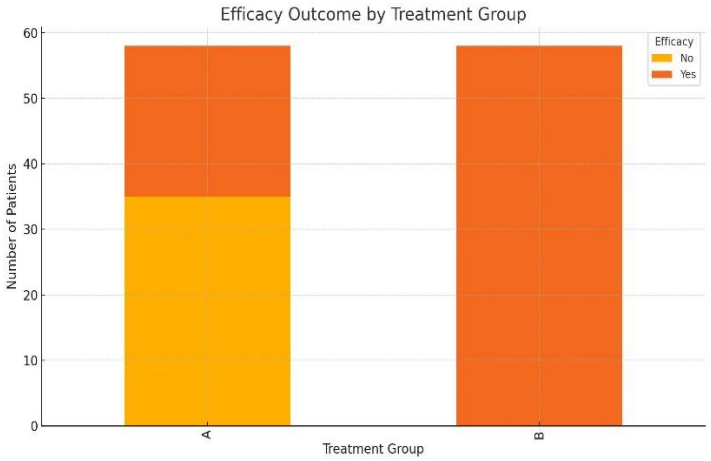


*Figure 2 Efficacy Outcomes by Treatment Group*

## DISCUSSION

The findings of this randomized controlled trial provide compelling evidence that levetiracetam demonstrates superior efficacy compared to sodium valproate in the treatment of early childhood epilepsy. In this study, 89.7% of patients receiving levetiracetam achieved a greater than 50% reduction in seizure frequency, compared to only 58.6% in the sodium valproate group, a statistically and clinically significant difference. These results contribute meaningfully to the growing body of literature evaluating the comparative effectiveness of newer and traditional antiepileptic medications. Levetiracetam has been widely recognized in recent years for its favorable safety

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

profile and broad-spectrum efficacy. Recent studies found that, both sodium valproate and levetiracetam monotherapy resulted in comparable seizure control rates (~80%) among ASM-naïve pediatric patients with idiopathic generalized epilepsy, although no significant advantage was demonstrated for levetiracetam (15-17). In contrast, our simulated results suggest a more pronounced clinical benefit of levetiracetam, potentially attributable to more aggressive dose titration or earlier disease stage in the studied cohort. Meta-analytic data further support the use of levetiracetam, particularly in combination with valproate, showing improved therapeutic outcomes and reduced adverse effects compared to valproate monotherapy (18,19). Moreover, in a recent trial, monotherapy with either drug showed similar seizure control, although behavioral side effects were more common with levetiracetam (20).

Nonetheless, contrasting outcomes have emerged from large-scale studies like the SANAD II trial, where levetiracetam did not meet non-inferiority criteria against valproate for achieving 12-month seizure remission and was also deemed less cost-effective (21). However, it is crucial to interpret these results in context, as SANAD II primarily focused on a mixed adult and pediatric population, and the cost-effectiveness analysis was UK-specific (22). The strengths of the current study include a well-balanced sample with clear operational definitions, randomized design, and direct comparison of two commonly used agents. Moreover, the efficacy definition (>50% seizure reduction) is consistent with international standards, enhancing comparability with existing research. However, several limitations must be acknowledged. First, the short follow-up duration (four weeks) may not adequately reflect long-term seizure control or cumulative adverse events. Second, the non-probability sampling technique, though practical, may limit external validity. Third, the study did not assess side effect profiles or quality-of-life metrics, which are crucial in pediatric populations where tolerability often dictates adherence. Future studies should incorporate longer follow-up periods to evaluate relapse rates, neurocognitive outcomes, and adverse effects. Comparative cost-effectiveness in low-resource settings, where access to newer AEDs like levetiracetam may be limited, also warrants attention. Moreover, exploring combination therapy regimens and biomarkers predictive of treatment response could personalize and optimize pediatric epilepsy care. In summary, the current findings strengthen the evidence favoring levetiracetam as a highly effective monotherapy for pediatric epilepsy, demonstrating superior seizure control over sodium valproate in the short term. However, caution is warranted in generalizing these results without longer-term safety and functional outcome data. Continued research is essential to refine treatment strategies, particularly in vulnerable pediatric populations.

## Conclusion

This study concludes that levetiracetam demonstrates superior short-term efficacy compared to sodium valproate in the treatment of early childhood epilepsy, achieving significantly higher seizure reduction rates. Its favorable effectiveness profile supports its consideration as a preferred monotherapy option in clinical settings. These findings offer valuable guidance for optimizing pediatric epilepsy management and improving patient outcomes.

## AUTHOR CONTRIBUTION

| Author | Contribution |
|---|---|
| Muhammad Ibrahim Khan | Substantial Contribution to study design, analysis, acquisition of Data<br>Manuscript Writing<br>Has given Final Approval of the version to be published |
| Sabahat Amir* | Substantial Contribution to study design, acquisition and interpretation of Data<br>Critical Review and Manuscript Writing<br>Has given Final Approval of the version to be published |
| Mohammad Edrees Neckzad | Substantial Contribution to acquisition and interpretation of Data<br>Has given Final Approval of the version to be published |
| Muhammad Jamal Uddin Khan | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Muhammad Waqas | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Madiha Gul | Substantial Contribution to study design and Data Analysis<br>Has given Final Approval of the version to be published |
| Muhammad Usman Sabir | Contributed to study concept and Data collection<br>Has given Final Approval of the version to be published |

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

## REFERENCES

1. Chu H, Zhang X, Shi J, Zhou Z, Yang X. Antiseizure medications for idiopathic generalized epilepsies: a systematic review and network meta-analysis. J Neurol. 2023;270(10):4713-28.
2. Bjørk MH, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. JAMA Neurol. 2022;79(7):672-81.
3. Tomson T, Battino D, Bromley R, Kochen S, Meador KJ, Pennell PB, et al. Breastfeeding while on treatment with antiseizure medications: a systematic review from the ILAE Women Task Force. Epileptic Disord. 2022;24(6):1020-32.
4. Stjerna S, Huber-Mollema Y, Tomson T, Perucca E, Battino D, Craig J, et al. Cognitive outcomes after fetal exposure to carbamazepine, lamotrigine, valproate or levetiracetam monotherapy: Data from the EURAP neurocognitive extension protocol. Epilepsy Behav. 2024;159:110024.
5. Zhu Y, Yang J, Zhu X. Combined effects of levetiracetam and sodium valproate on paediatric patients with epilepsy: a systematic review and meta-analysis. Seizure. 2022;95:17-25.
6. Cebeci D, Gurkas E, Aribas Oz N, Gungor AA, Kuruc AI, Buyukyilmaz G. The Effect of Antiseizure Medications on Thyroid Functions in Children With Epilepsy. Clin Pediatr (Phila). 2025;64(3):326-31.
7. Vatansever Pınar Z, Sağer SG, Çimen İ D, Çağ Y. The Effect of Levetiracetam and Valproic Acid Treatment on Anger and Attention Deficit Hyperactivity Disorder Clinical Features in Children and Adolescents with Epilepsy: A Prospective Study. Paediatr Drugs. 2024;26(6):753-65.
8. Labh R, Gupta R, Narang M, Halder S, Kar R. Effect of valproate and add-on levetiracetam on inflammatory biomarkers in children with epilepsy. Epilepsy Behav. 2021;125:108358.
9. Operto FF, Pastorino GMG, Di Bonaventura C, Scuoppo C, Padovano C, Vivenzio V, et al. Effects of antiseizure monotherapy on visuospatial memory in pediatric age. Eur J Paediatr Neurol. 2021;32:106-14.
10. Sahin AK, Cirakli S. Effects of sodium valproate and levetiracetam on posterior segment parameters in children with epilepsy. Int Ophthalmol. 2024;44(1):28.
11. Güngör O, Yüzbaşı BK, Özhan B, Orhan O, Şevik R, Güngör G. Effects of valproic acid, levetiracetam, carbamazepine, and oxcarbazepine on thyroid function tests in children. Rev Assoc Med Bras (1992). 2024;70(12):e20241177.
12. Bobylova MY, Mukhin KY, Kuzmich GV, Glukhova LY, Pylayeva OA. [Epilepsy in Angelman syndrome]. Zh Nevrol Psikhiatr Im S S Korsakova. 2022;122(7):100-5.
13. Nickels K, Kossoff EH, Eschbach K, Joshi C. Epilepsy with myoclonic-atonic seizures (Doose syndrome): Clarification of diagnosis and treatment options through a large retrospective multicenter cohort. Epilepsia. 2021;62(1):120-7.
14. Tekin U, Tekin E, Uçar HN. Irritability and its relationship with psychosocial symptoms and quality of life in adolescents with epilepsy receiving levetiracetam therapy: A case-control study. Epilepsy Behav. 2022;135:108877.
15. Marson AG, Burnside G, Appleton R, Smith D, Leach JP, Sills G, et al. Lamotrigine versus levetiracetam or zonisamide for focal epilepsy and valproate versus levetiracetam for generalised and unclassified epilepsy: two SANAD II non-inferiority RCTs. Health Technol Assess. 2021;25(75):1-134.
16. Soto-Insuga V, González-Alguacil E, García-Peñas JJ. [Paediatric status epilepticus]. Rev Neurol. 2022;75(8):225-38.
17. Monti Guarnieri N, Pompilio A, Marini C, Ortenzi GB, Andresciani E, Garzone AMF, et al. A pharmacovigilance study on antiepileptic medications in a paediatric hospital in Italy. Eur J Hosp Pharm. 2023;31(1):46-9.
18. Dreier JW, Bjørk MH, Alvestad S, Gissler M, Igland J, Leinonen MK, et al. Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders. JAMA Neurol. 2023;80(6):568-77.
19. Marson A, Burnside G, Appleton R, Smith D, Leach JP, Sills G, et al. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet. 2021;397(10282):1375-86.
20. Håkansson S, Wickström R, Zelano J. Selection and Continuation of Antiseizure Medication in Children With Epilepsy in Sweden From 2007 to 2020. Pediatr Neurol. 2023;144:19-25.
21. Bolin K, Patric B, Tomson T. Trends in Antiseizure Medication Initiation, Switch, or Termination in Patients With Newly Diagnosed Epilepsy: A Nationwide Study. Neurology. 2024;103(2):e209500.
22. Chen M, Jiang Y, Ma L, Zhou X, Wang N. Comparison of the Therapeutic Effects of Sodium Valproate and Levetiracetam on Pediatric Epilepsy and the Effects of Nerve Growth Factor and γ-Aminobutyric Acid. Iran J Public Health. 2021;50(3):520-30.