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Comparative Effects of Valproic Acid and Levetiracetam Monotherapy on Cognitive Function in Children with Newly Diagnosed Epilepsy: A Prospective Observational Study

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Abstract

Background

Antiseizure medications may differ in their effects on seizure control, tolerability, and cognitive performance, which is particularly relevant in children with newly diagnosed epilepsy. This study compared the short-term effectiveness, tolerability, and cognitive screening outcomes of levetiracetam and valproic acid monotherapy in pediatric epilepsy.

Methods

This prospective, single-center observational cohort study included 60 children aged 3–14 years with newly diagnosed epilepsy who had not previously received antiseizure medication. Participants received levetiracetam (n = 30) or valproic acid (n = 30) monotherapy according to routine clinical practice. Seizure frequency, adverse drug reactions, and cognitive screening outcomes were assessed at baseline and after 12 weeks. Cognitive status was evaluated using the Modified Mini-Mental State Examination (Modified MMSE), which was interpreted as a brief screening instrument rather than a comprehensive neuropsychological assessment. Within- and between-group comparisons were performed using appropriate statistical tests.

Results

Baseline demographic and clinical characteristics were comparable between groups. After 12 weeks, mean Modified MMSE scores increased from 25.00 ± 1.43 to 26.80 ± 1.64 in the levetiracetam group and decreased from 25.70 ± 1.53 to 24.43 ± 1.57 in the valproic acid group (both $p < 0.001$). The post-treatment score was higher with levetiracetam than valproic acid (26.80 ± 1.64 vs. 24.43 ± 1.57; $p < 0.001$). Seizure frequency decreased in both groups, with no significant between-group difference at 12 weeks. Adverse drug reactions were reported in 26.7% of children receiving levetiracetam compared with 80.0% receiving valproic acid ($p < 0.001$).

Conclusions

Over 12 weeks, both treatments were associated with reduced seizure frequency, with no significant between-group difference. Levetiracetam was associated with higher cognitive screening scores and fewer reported adverse drug reactions than valproic acid. These findings should be interpreted cautiously given the small sample, single-center observational design, short follow-up, potential residual confounding, and use of a brief cognitive screening instrument. Larger multicenter studies using validated, age-appropriate neuropsychological assessments are warranted.

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by a predisposition to recurrent unprovoked seizures and is one of the most common neurological disorders worldwide. The International League Against Epilepsy (ILAE) defines epilepsy on the basis of at least two unprovoked seizures occurring more than 24 h apart, one unprovoked seizure associated with a sufficiently high probability of recurrence, or the diagnosis of an epilepsy syndrome [1]. Approximately 50 million people worldwide are affected by epilepsy, representing a substantial global health burden [2]. In children, epilepsy is particularly important because recurrent seizures and the underlying neurological disorder may affect learning, behavior, neurodevelopment, and quality of life. Pediatric epilepsy has also been associated with increased morbidity and mortality compared with the general pediatric population [3].

Antiseizure medications (ASMs) constitute the mainstay of pharmacological management and are often prescribed for prolonged periods [4]. In children, selection of an ASM requires consideration of seizure control together with tolerability and potential effects on cognitive and behavioral functioning. Cognitive difficulties in pediatric epilepsy may arise from multiple factors, including the underlying epilepsy, seizure burden, epileptiform activity, developmental characteristics, and associated behavioral or learning problems [5–9]. In addition, ASM exposure may contribute to cognitive or behavioral changes, making it clinically relevant to evaluate treatment-related outcomes alongside seizure control [10].

The cognitive and behavioral effects of ASMs may vary according to their pharmacological properties. Antiseizure agents act through different mechanisms that reduce neuronal excitability or enhance inhibitory neurotransmission, and these effects may influence attention, memory, alertness, and other aspects of behavior and cognition [11]. Such effects may be particularly relevant in children because treatment occurs during a period of continuing cognitive and neurological development [12]. Consequently, comparative evaluation of commonly used ASMs is important when considering the overall balance between seizure control, tolerability, and potential effects on cognitive functioning.

Levetiracetam and valproic acid are established ASMs used in the treatment of epilepsy, but they have distinct pharmacological and adverse-effect profiles. Previous clinical studies have reported differences in cognitive and behavioral outcomes between these agents, although results have varied according to patient population, epilepsy characteristics, treatment duration, and assessment methods [15–18]. In particular, the extent to which observed cognitive differences are attributable to the medication itself rather than the underlying characteristics of epilepsy remains uncertain.

Assessment of cognition in children presents additional methodological challenges because cognitive performance changes substantially with age and developmental stage. The Modified Mini-Mental State Examination (Modified MMSE) has previously been described as a brief screening instrument for cognitive functions in Indian pediatric populations [14]. In the present study, it was used as a pragmatic measure of global cognitive screening. However, it should not be considered equivalent to a comprehensive, age-appropriate neuropsychological assessment, and the results therefore require cautious interpretation.

The present study was designed as a prospective observational comparison of levetiracetam and valproic acid monotherapy in children with newly diagnosed epilepsy. We evaluated seizure frequency, adverse drug reactions, and changes in Modified MMSE scores over a 12-week period. Because treatment allocation was non-randomized and the study was conducted at a single center with a relatively small sample, the study was intended to provide preliminary comparative clinical data rather than establish causal differences between the two treatments. In addition, recognizing that epilepsy-related clinical characteristics may influence both treatment response and cognitive outcomes, the findings were interpreted in the context of the available baseline demographic and seizure-related characteristics.

MATERIALS AND METHODS

Study Design and Setting

This prospective, observational, non-interventional cohort study was conducted in the Department of Paediatrics, Owaisi Hospital and Research Centre, Hyderabad, Telangana, India, from November 2024 to April 2025. The study was approved by the Institutional Ethics Committee of Owaisi Hospital and Research Centre (IEC No. 2025/61/069). Written informed consent was obtained from the parents or legal representatives of all participants before enrolment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Participants

Children aged 3–14 years with newly diagnosed epilepsy according to International League Against Epilepsy (ILAE) criteria and with no previous exposure to antiseizure medication were eligible for participation.

Children receiving polytherapy or medications considered capable of substantially affecting cognitive function were excluded. Additional exclusion criteria included hypersensitivity to either study medication, significant hepatic or renal impairment, and pre-existing cognitive disorders that could independently influence cognitive assessment or treatment tolerability.

Treatment Groups and Treatment Regimens

Participants received either levetiracetam or valproic acid as monotherapy according to routine clinical decision-making. Treatment allocation was therefore not randomized and was determined clinically according to the treating physician's assessment. This aspect of the study design was considered when interpreting between-group differences.

Both medications were initiated at 20 mg/kg/day and subsequently titrated at 2-week intervals according to clinical response and tolerability. The mean final maintenance doses were 30.00 ± 6.90 mg/kg/day for

levetiracetam and 29.20 ± 7.70 mg/kg/day for valproic acid. Participants were followed clinically for 12 weeks after treatment initiation.

Baseline Clinical Assessment

Baseline demographic and clinical information was collected using structured interviews and review of clinical records. Variables included age, sex, educational level, socioeconomic status, family history of epilepsy, age at seizure onset, seizure type, seizure frequency, seizure duration, and relevant comorbidities.

Seizure type was classified as focal or generalized according to the available clinical assessment and the 2017 ILAE classification framework. Electroencephalography (EEG) was performed as part of the clinical evaluation to support seizure classification. Baseline seizure frequency was recorded before initiation of antiseizure therapy.

The available dataset did not include detailed epilepsy syndrome classification or a comprehensive characterization of etiological factors. These limitations were considered during interpretation of the findings.

Cognitive Screening Assessment

Cognitive performance was assessed at baseline and after 12 weeks using the Modified Mini-Mental State Examination (Modified MMSE), previously described for assessment of cognitive functions in Indian pediatric populations [14]. *The instrument evaluates broad cognitive domains including orientation, attention and concentration, registration, recall, and language.*

Because the Modified MMSE is a brief screening instrument rather than a comprehensive age-specific neuropsychological battery, its results in the present study were interpreted as measures of cognitive screening performance rather than definitive measures of global neurocognitive function. Comprehensive standardized pediatric neuropsychological assessments were not available within the study setting. Accordingly, changes in Modified MMSE scores were considered exploratory outcomes.

Outcome Measures

The cognitive screening outcome was assessed by comparing Modified MMSE scores at baseline and after 12 weeks of treatment.

Secondary outcomes included seizure frequency and treatment-related adverse drug reactions. Seizure frequency was recorded at baseline and after 12 weeks of therapy. Adverse events occurring during treatment were documented during follow-up and categorized according to the clinical presentation, including irritability, hyperactivity, fatigue, aggression, headache, altered sleep, hair loss, nausea, weight gain, and anorexia.

Statistical Analysis

Data were initially entered into Microsoft Excel and subsequently analyzed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation when appropriate, while categorical variables were presented as frequencies and percentages. Seizure frequency data were expressed as median and interquartile range where appropriate.

Between-group comparisons of continuous variables were performed using the Mann–Whitney U test, and within-group changes from baseline to 12 weeks were assessed using the Wilcoxon signed-rank test. Categorical variables, including adverse drug reactions and other categorical clinical outcomes, were compared using the chi-square test or Fisher's exact test, as appropriate. A two-sided p-value < 0.05 was considered statistically significant.

Where available, effect sizes and 95% confidence intervals were reported to describe the magnitude and precision of observed differences. No formal a priori sample-size or power calculation was performed; the study included 60 participants, with 30 participants in each treatment group. The relatively small sample size limits the statistical power of the study, particularly for detecting small between-group differences.

Because treatment assignment was observational and the sample size was limited, no multivariable adjustment was undertaken. Consequently, residual confounding from measured and unmeasured clinical characteristics cannot be excluded.

Reporting Considerations

The study was reported with consideration of the principles of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Given the observational design, findings were interpreted as associations rather than evidence of a causal effect of either antiseizure medication on cognitive or clinical outcomes.

RESULTS

Participant Baseline and Clinical Characteristics

A total of 60 children with newly diagnosed epilepsy were included in the study, with 30 receiving valproic acid and 30 receiving levetiracetam monotherapy. Baseline demographic and clinical characteristics are presented in Table 1. The mean age was 6.30 ± 2.89 years in the valproic acid group and 6.40 ± 3.18 years in the levetiracetam group, with no statistically significant difference between groups (p = 0.90). The sex distribution was also comparable, with 17 males (56.6%) and 13 females (43.3%) in the valproic acid group and 16 males (53.3%) and 14 females (46.6%) in the levetiracetam group (p = 0.79).

The distribution of educational level, family history of epilepsy, socioeconomic status, seizure duration, and seizure type did not differ significantly between the treatment groups. Focal seizures were reported

in 14 (47%) children in the valproic acid group and 17 (57%) in the levetiracetam group, whereas generalized seizures were reported in 16 (53%) and 13 (43%), respectively (p = 0.43). Overall, the measured baseline characteristics were broadly comparable between the two groups.

Cognitive Screening Outcomes

Changes in Modified Mini-Mental State Examination (Modified MMSE) scores from baseline to 12 weeks are presented in Table 2. In the levetiracetam group, the mean total Modified MMSE score increased from 25.00 ± 1.43 at baseline to 26.80 ± 1.64 at 12 weeks, corresponding to a mean increase of 1.80 points (95% CI, 1.24–2.36; Cohen's d = 1.17; p < 0.001).

In the valproic acid group, the mean total Modified MMSE score decreased from 25.70 ± 1.53 at baseline to 24.43 ± 1.57 at 12 weeks, representing a mean change of − 1.27 points (95% CI, − 1.83 to − 0.71; Cohen's d = 0.82; p < 0.001). Within the valproic acid group, the orientation, registration and sensory perception, recall, and language domains showed statistically significant changes, whereas attention and concentration did not (Table 2). In the levetiracetam group, statistically significant changes were observed across the assessed domains.

At 12 weeks, the mean total Modified MMSE score was higher in the levetiracetam group than in the valproic acid group (26.80 ± 1.64 vs. 24.43 ± 1.57), with a between-group difference of 2.37 points (95% CI, 1.56–3.18; Cohen's d = 1.48; p < 0.001). Domain-level comparisons showed statistically significant between-group differences in orientation, registration and sensory perception, recall, and language, while the difference in attention and concentration was not statistically significant (Table 3).

Because the Modified MMSE was used as a brief cognitive screening instrument, these findings represent differences in screening scores and should not be interpreted as evidence of changes in comprehensive neuropsychological functioning.

Safety and Tolerability

Adverse drug reactions were reported in 24 of 30 children (80.0%) receiving valproic acid and in 8 of 30 children (26.7%) receiving levetiracetam. The difference in the proportion of participants without reported adverse drug reactions was statistically significant (p < 0.001). The reported adverse events and their frequencies are summarized in Table 4.

Headache was reported in 7 children (23.3%) receiving valproic acid and none of the children receiving levetiracetam (p = 0.01). Increased sleep was reported in 4 children (13.3%) in the valproic acid group, while hair loss, nausea, weight gain, and decreased sleep were reported only in the valproic acid group. Irritability was reported in 2 children (6.7%) receiving valproic acid and 4 children (13.3%) receiving levetiracetam, while hyperactivity was reported in 2 children (6.7%) in the levetiracetam group. Fatigue occurred in 1 child (3.3%) in each group, and aggression was reported in 1 child (3.3%) receiving levetiracetam.

Overall, 6 children (20.0%) in the valproic acid group and 22 children (73.3%) in the levetiracetam group reported no adverse drug reactions during the 12-week follow-up ($p < 0.001$). Given the observational treatment allocation, these differences should be interpreted as between-group associations rather than definitive evidence of differential drug-related risk.

Seizure Frequency

Seizure frequency at baseline and after 12 weeks of treatment is presented in Table 5. At baseline, the median seizure frequency was 2 (IQR, 1–2) seizures per week in the valproic acid group and 1.5 (IQR, 1–2) seizures per week in the levetiracetam group, with no statistically significant between-group difference ($p = 0.34$).

After 12 weeks, the median seizure frequency was 1 (IQR, 1–2) seizure per week in the valproic acid group and 1 (IQR, 1–1) seizure per week in the levetiracetam group. The between-group difference at 12 weeks was not statistically significant ($p = 0.79$). Thus, both treatment groups demonstrated lower median seizure frequency during follow-up, with no statistically significant difference between groups at the end of the observation period.

Table 1
sociodemographic profile and baseline parameters of both groups

Demographic profile		**Valproic acid (n = 30)**	**Levetiracetam (n = 30)**	**p-value (0.05)**
Age in years		6.30 ± 2.89*	6.40 ± 3.18*	0.90
Gender	Male	17 (56.6%)	16 (53.3%)	0.79
	Female	13 (43.3%)	14 (46.6%)	
Educational level	Primary	24 (80%)	25 (83.3%)	0.73
	Secondary	6 (20%)	5 (16.7%)	
Family history	Present	16 (53.3%)	19 (63.3%)	0.43
	Absent	14 (46.7%)	11 (36.7%)	
Socio-economic status	Lower	16 (53.3%)	14 (46.7%)	0.85
	Middle	10 (33.3%)	12 (40%)	
	Upper	4 (13.3%)	4 (13.33%)	
Seizure duration	< 2 mins	4 (13.3%)	0 (0%)	0.46
	2-5 Mins	17 (56.7%)	21 (70%)	
	> 5 mins	9 (30%)	9 (30)	
Seizure type	Focal	14 (47%)	17 (57%)	0.43
	Generalized	16 (53%)	13 (43%)	

Data presented as *mean ± SD (continuous) compared by independent t-test and n / % (categorical) compared by Chi-square test.

MMSE Score for cognitive outcomes: In the levetiracetam group, significant improvements were observed in MMSE domains over 12 weeks, particularly in all domains ($p < 0.05$). The total MMSE score increased from 25.00 ± 1.43 at baseline to 26.80 ± 1.64 at 12 weeks with a mean increase of 1.80 (95% CI: 1.24–2.36; Cohen's d = 1.17) which is statistically significant ($p < 0.001$) as in table2.

Table :2 Comparison analysis of Intra- Group baseline and 12 weeks modified MMSE Scores in both the groups

Parameter	Group	Baseline	12 weeks	p-value (0.05)
1. Orientation	Valproic Acid	9.00 ± 0.87	8.33 ± 1.02	< 0.001***
	Levetiracetam	8.83 ± 1.08	9.17 ± 0.95	0.008**
2. Attention and Concentration	Valproic Acid	4.67 ± 0.92	4.77 ± 0.97	0.43
	Levetiracetam	4.57 ± 0.62	4.97 ± 0.76	< 0.001**
3. Registration and Sensory Perception	Valproic Acid	2.37 ± 0.61	2.17 ± 0.53	0.01*
	Levetiracetam	2.17 ± 0.53	2.63 ± 0.49	0.002**
4. Recall	Valproic Acid	2.63 ± 0.55	2.23 ± 0.54	0.003**
	Levetiracetam	2.47 ± 0.62	2.83 ± 0.46	< 0.001***
5. Language	Valproic Acid	7.03 ± 0.55	6.83 ± 0.64	0.01*
	Levetiracetam	6.87 ± 0.68	7.20 ± 0.55	0.002**
6. Total MMSE	Valproic Acid	25.70 ± 1.53	24.43 ± 1.57	< 0.001***
	Levetiracetam	25.00 ± 1.43	26.80 ± 1.64	< 0.001***

The data is displayed as mean ± SD. Wilcoxon signed-rank test is used to evaluate P-values; **p < 0.01 significant, ***<0.001 highly significant.

At 12 weeks of treatment, there was no discernible improvement in cognitive function in the valproic acid group, and orientation significantly declined (p < 0.0001). The overall MMSE score decreased statistically significance from baseline 25.70 ± 1.53 to 24.43 ± 1.57 after treatment with mean difference of 1.27 (95% CI: -1.83-0.71; Cohen's d = 0.82) which is statistically significant (p < 0.001).

Post-treatment MMSE values were considerably greater in levetiracetam group than in valproic acid group across most categories (24.43 ± 1.57 vs. 26.80 ± 1.64), with a mean difference of 2.37 (95% CI: 1.56–3.18; d = 1.48) which is statistically significant (p < 0.001) suggesting a meaningful change in cognitive performance (p < 0.05) with levetiracetam as shown in Table 3 and fig-1

Table 3
Comparison evaluation of total MMSE scores of levetiracetam and valproic acid post-treatment at 12 weeks

Parameter	Valproic Acid (n = 30)	Levetiracetam (n = 30)	p-value (0.05)
1. Orientation	8.33 ± 1.02	9.17 ± 0.95	< 0.001**
2. Attention and Concentration	4.77 ± 0.97	4.97 ± 0.76	0.40
3. Registration and Sensory Perception	2.17 ± 0.53	2.63 ± 0.49	0.001*
4. Recall	2.33 ± 0.54	2.83 ± 0.46	< 0.001**
5. Language	6.83 ± 0.64	7.20 ± 0.55	0.009*
6. Total MMSE	24.43 ± 1.57	26.80 ± 1.64	< 0.001**

Data presented as mean ± SD. p-values analysis by the Mann-Whitney U test. *p < 0.05 statistically significant; **p < 0.0001 highly significant.

Fig-1 Comparison of mean MMSE scores from baseline to post treatment period between valproic acid and levetiracetam.

Safety and Tolerability Assessment: Adverse events occurred significantly less frequently in the levetiracetam group, in 26.4% of patients. In contrast, 80% of patients in the valproic acid group experienced adverse effects with a chi-square value of $x^2 = 16.7$ (df = 1, p < 0.001) and odds ratio of 11.0 (95% CI: 3.3–36.5), indicating a markedly increased risk of ADRs in valproic acid group as presented in Table 4 and fig-2. This finding suggests that the observed adverse effects are more likely attributable to drug exposure rather than the pre-existing disease burden.

Table 4
comparison of adverse effects between both groups at 12 weeks post-treatment

Adverse effect	Valproic Acid (n = 30)	%	Levetiracetam (n = 30)	%	p- value (0.05)
1.Irritability	2	6.7%	4	13.3%	0.67
2.Hyperactivity	0	0%	2	6.7%	0.50
3.Fatigue	1	3.3%	1	3.3%	1.00
4.Aggression	0	0%	1	3.3%	1.00
5.Headache	7	23.3%	0	0%	0.01*
6.Increased sleep	4	13.3%	0	0%	0.11
7.Hairfall	3	10%	0	0%	0.24
8.Nausea	2	6.7%	0	0%	0.49
9.Weight gain	2	6.7%	0	0%	0.49
10.Decreased sleep	2	6.7%	0	0%	0.49
11.Anorexia	1	3.3%	0	0%	1.00
12.Nil (no ADR)	6	20%	22	73.3%	< 0.001**

Data are presented as n (%), and the Fisher's Exact Test was used for comparisons. *p < 0.05 was considered as significant, whereas **p < 0.001 indicated high significance.

Fig-2 Comparison of tolerability profile between valproic acid and levetiracetam

Seizure Frequency Reduction- Both levetiracetam and valproic acid indicates no significant difference in seizure frequency reduction after 12 weeks (p = 0.53; 95% CI: -0.22-0.42; d = 0.16), indicating minimal between-group variation (Table 5).

Table 5
comparison of seizure frequency reduction between valproic acid and levetiracetam at baseline and 12 weeks of treatment

Seizure frequency (Per Week)	Valproic acid (n = 30)	Levetiracetam (n = 30)	p-value
Baseline	2 [1–2]	1.5 [1–2]	0.34
12 weeks	1 [1–2]	1 [1–1]	0.79

Data expressed as Median (IQR), comparisons were done using Mann-Whitney

DISCUSSION

Principal findings

In this prospective observational cohort of children with newly diagnosed epilepsy, both levetiracetam and valproic acid were associated with a reduction in seizure frequency over 12 weeks, with no statistically significant between-group difference at follow-up. In contrast, the two groups differed in their cognitive screening outcomes and tolerability profiles. The mean Modified Mini-Mental State Examination (Modified MMSE) score increased in the levetiracetam group and decreased in the valproic acid group. Adverse events were also reported less frequently among children receiving levetiracetam. Because treatment allocation was non-randomized, these findings represent observed associations and should not be interpreted as evidence of a causal treatment effect.

Comparison with recent clinical evidence

The comparable short-term seizure-frequency outcomes observed in our cohort are consistent with a recent randomized controlled trial involving 116 children with new-onset epilepsy. That study found no significant difference between levetiracetam and valproate in seizure control over three consecutive months or in the proportion achieving at least a 50% reduction in seizure frequency. However, weight gain was significantly lower with levetiracetam.

Evidence from other pediatric populations indicates that comparative efficacy may depend on epilepsy phenotype. A randomized study of 211 children with generalized epilepsy reported longer seizure-free duration and higher six-month seizure-free rates with valproate than with levetiracetam. Similarly, the SANAD II trial reported that levetiracetam did not demonstrate non-inferiority to valproate for long-term remission in patients with generalized or unclassified epilepsy. These findings are relevant because the present cohort included both focal and generalized seizures but lacked detailed epilepsy-syndrome and etiological classification. Therefore, the absence of a significant difference in our study should be interpreted as a finding within this mixed cohort rather than evidence of equivalent efficacy across epilepsy syndromes.

The lower overall frequency of adverse events observed with levetiracetam is also broadly consistent with contemporary comparative evidence. In our cohort, headache, increased sleep, hair loss, nausea, weight gain, and decreased sleep were reported only in the valproic acid group, whereas irritability and hyperactivity occurred more frequently with levetiracetam. However, the small sample size limits reliable comparison of individual adverse events, and the observed differences should therefore be considered descriptive.

Cognitive screening outcomes

The higher Modified MMSE scores observed with levetiracetam are consistent in direction with previous reports suggesting a relatively favorable cognitive profile for levetiracetam compared with valproate, although the available evidence remains heterogeneous. A 2024 systematic review and meta-analysis of

16 double-blind randomized placebo-controlled trials involving 545 participants found an association between levetiracetam and improved executive-function measures compared with placebo, while also highlighting heterogeneity and potential publication bias. The authors therefore considered the evidence exploratory rather than definitive.

The interpretation of our findings is further complicated by differences in cognitive assessment methods and epilepsy populations. Recent pediatric research has shown that cognitive outcomes may remain stable with both levetiracetam and valproate when assessed using domain-specific, age-appropriate instruments. Such differences emphasize that cognitive effects may vary according to the cognitive domain examined, underlying epilepsy syndrome, duration of treatment, and characteristics of the assessment instrument.

Accordingly, the present results should be interpreted specifically as differences in **cognitive screening scores** rather than evidence of improvement or deterioration in comprehensive neuropsychological functioning. The Modified MMSE provides a brief global assessment but does not encompass the breadth of standardized pediatric neuropsychological testing, particularly for executive function, processing speed, and other age-dependent cognitive domains. This limitation is particularly relevant to the present cohort, which included children from 3 to 14 years of age.

Pharmacological considerations

The observed differences are biologically plausible in view of the distinct pharmacological properties of the two antiseizure medications, although the present study cannot establish specific mechanisms. Levetiracetam primarily acts through binding to synaptic vesicle protein 2A (SV2A), whereas valproic acid has multiple pharmacological actions involving inhibitory and excitatory neurotransmission and voltage-gated ion channels. Levetiracetam also has relatively limited hepatic metabolism and a low potential for pharmacokinetic drug interactions, whereas valproic acid has a broader systemic adverse-effect profile that includes somnolence and weight gain.

These pharmacological differences may contribute to variation in tolerability between the agents. Nevertheless, the cognitive findings cannot be attributed solely to the molecular mechanism of either medication. Cognitive performance in pediatric epilepsy is influenced by multiple factors, including seizure burden, epilepsy characteristics, developmental stage, behavioral comorbidity, treatment effects, and learning environment. The present observational design and limited clinical characterization therefore preclude mechanistic conclusions.

Clinical implications

Selection of initial antiseizure therapy in children should be individualized according to seizure type and epilepsy syndrome, expected efficacy, tolerability, comorbidities, developmental considerations, and patient and family preferences. The present findings suggest that levetiracetam may offer a favorable short-term tolerability profile and may be associated with higher cognitive screening scores in children

with newly diagnosed epilepsy. However, these observations do not establish levetiracetam as universally preferable to valproic acid.

This distinction is important because contemporary evidence suggests that valproate may provide superior seizure control in some generalized epilepsies. Thus, the potential advantages of one medication in terms of tolerability or cognitive screening should be considered alongside the specific epilepsy phenotype and the need to achieve optimal seizure control.

Strengths and limitations

The prospective design, inclusion of treatment-naïve children, use of monotherapy, and predefined 12-week follow-up are strengths of the study. Assessment of seizure frequency, cognitive screening, and adverse events within the same cohort also provides an integrated comparison of several clinically relevant treatment outcomes.

Several limitations should be considered. The study was conducted at a single center and included only 60 participants, limiting statistical power and generalizability. Treatment allocation was non-randomized and based on routine clinical practice, creating the possibility of selection bias and confounding by indication. Although measured baseline demographic and seizure characteristics were broadly comparable, detailed epilepsy syndrome, etiology, developmental status, EEG characteristics, adherence, and other potentially relevant determinants of cognitive and seizure outcomes were not comprehensively characterized or statistically adjusted for.

The 12-week follow-up also limits assessment of long-term cognitive, developmental, metabolic, and safety outcomes. In addition, the Modified MMSE was used as a brief cognitive screening instrument rather than a comprehensive, age-specific neuropsychological battery. The observed differences should therefore be regarded as exploratory. Finally, multiple cognitive domains and individual adverse events were evaluated in a small sample, increasing the possibility of unstable estimates and chance findings.

Overall, the findings indicate that levetiracetam and valproic acid were associated with similar short-term reductions in seizure frequency in this small mixed pediatric epilepsy cohort, while levetiracetam was associated with higher cognitive screening scores and fewer reported adverse events. These findings are consistent with a possible difference in short-term tolerability and cognitive screening profiles, but they do not establish treatment superiority or therapeutic equivalence.

Future multicenter studies should enroll larger and better-characterized pediatric populations, classify epilepsy syndromes and etiologies in greater detail, use validated age-appropriate neuropsychological instruments, incorporate longer follow-up, and apply appropriate methods to control for confounding. Such studies are needed to determine whether the differences observed in cognitive screening and tolerability represent reproducible treatment effects.

CONCLUSION

In this prospective observational cohort of children with newly diagnosed epilepsy, levetiracetam and valproic acid were associated with reductions in seizure frequency over 12 weeks, with no statistically significant between-group difference in seizure frequency at follow-up. Levetiracetam was associated with higher Modified MMSE cognitive screening scores and fewer reported adverse drug reactions than valproic acid. However, these findings should be interpreted cautiously because of the small sample size, single-center setting, non-randomized treatment allocation, short follow-up period, incomplete characterization of epilepsy-related clinical factors, and reliance on a brief cognitive screening instrument. The findings therefore remain preliminary and should not be interpreted as evidence that levetiracetam improves cognition or is universally superior to valproic acid. Larger, multicenter prospective or randomized studies incorporating detailed epilepsy characterization, longer follow-up, and validated age-appropriate neuropsychological assessments are needed to clarify the comparative cognitive, safety, and antiseizure effects of these treatments in children.

Declarations

Author's Contribution:

Habib Pathan (Study conception and design, manuscript editing, and language proofreading).

Zeenath Unnissa (Study design and conceptualization, manuscript editing and proofreading, final approval of the manuscript, and accountability for all aspects of the work).
Ayesha Nazneen (Data retrieval, manuscript drafting, and editing).
Soha Amreen (Data retrieval, manuscript drafting, and editing).
Shaik Nousheen (Data retrieval, manuscript drafting, and editing).

Aasia Sultana (Data retrieval, manuscript drafting, and editing).

Competing Interest

The authors report that there are no conflicts of interest.

Financial Support

This study was conducted without any external funding support.

Ethical Approval

The study was conducted according to the ethical principles of Declaration of Helsinki and was approved by the Institutional Ethics Committee of Owaisi Hospital and Research Centre, Hyderabad, Telangana, India (IEC No. 2025/61/069).

Informed Consent Form

Written informed consent was obtained from all the legal guardians of participants included in the study.

Consent to Publish

Not Applicable

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Figures

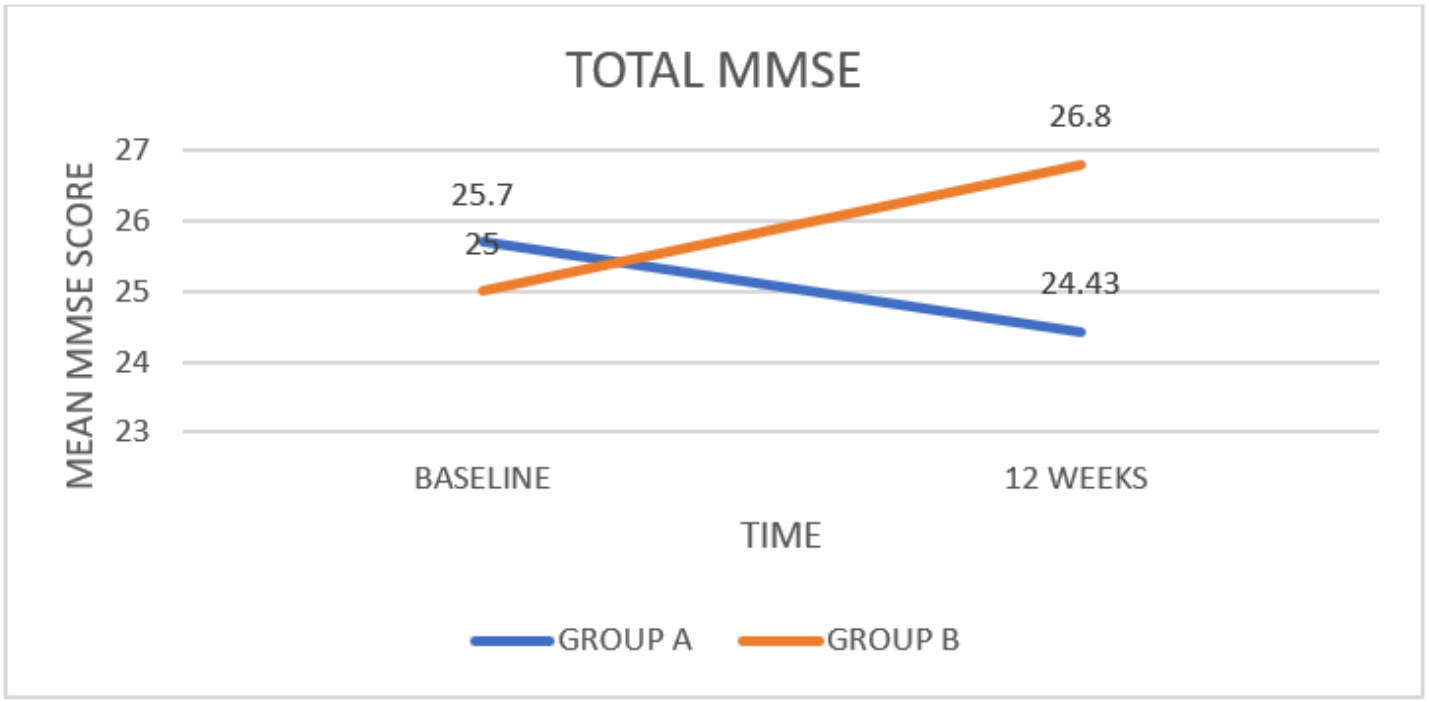


Figure 1

Comparison of mean MMSE scores from baseline to post treatment period between valproic acid and levetiracetam.

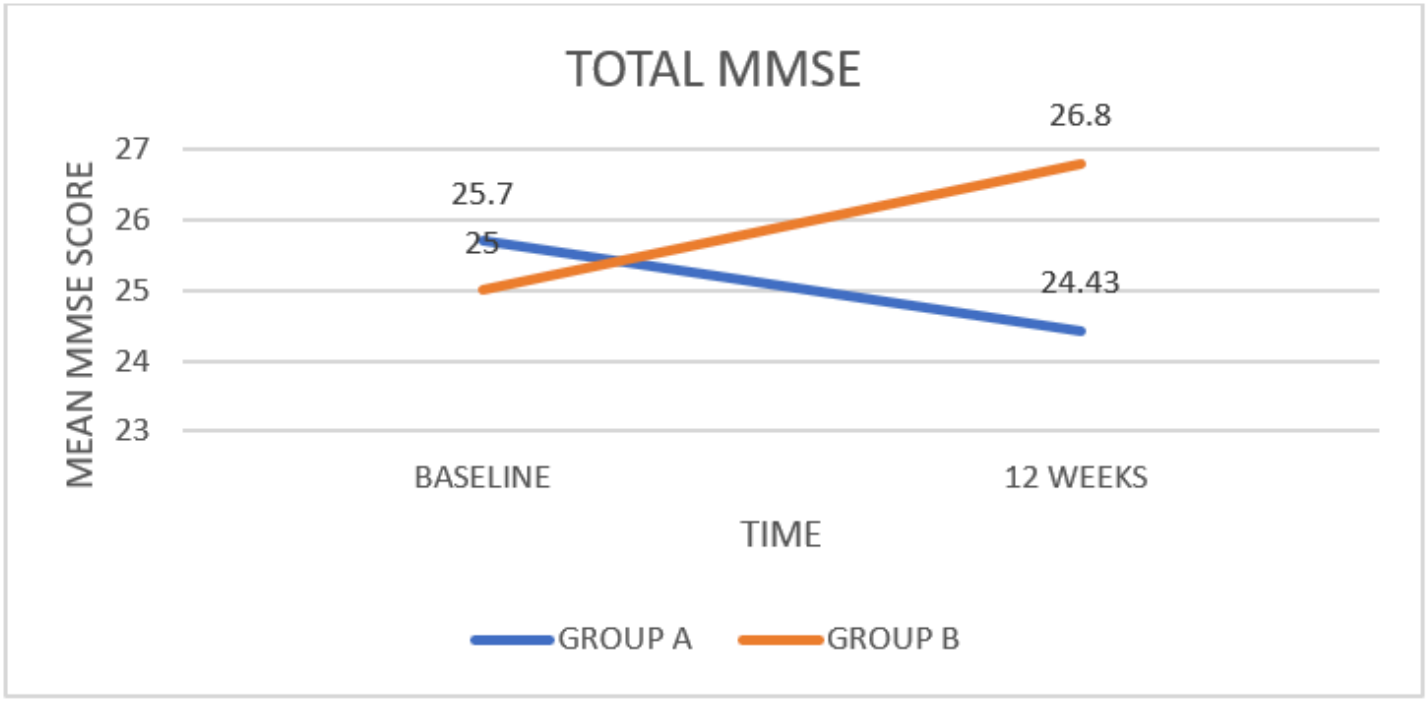


Figure 1

Comparison of mean MMSE scores from baseline to post treatment period between valproic acid and levetiracetam.

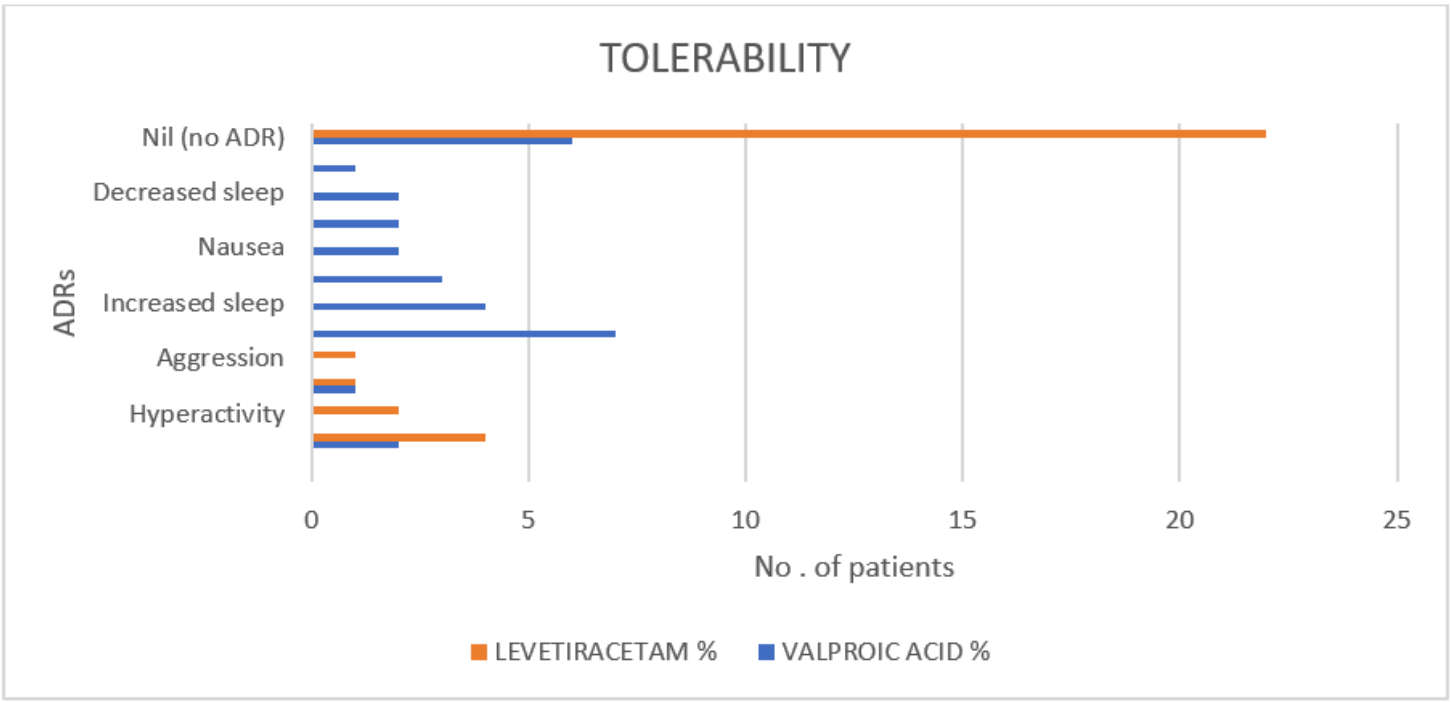


Figure 2

Comparison of tolerability profile between valproic acid and levetiracetam

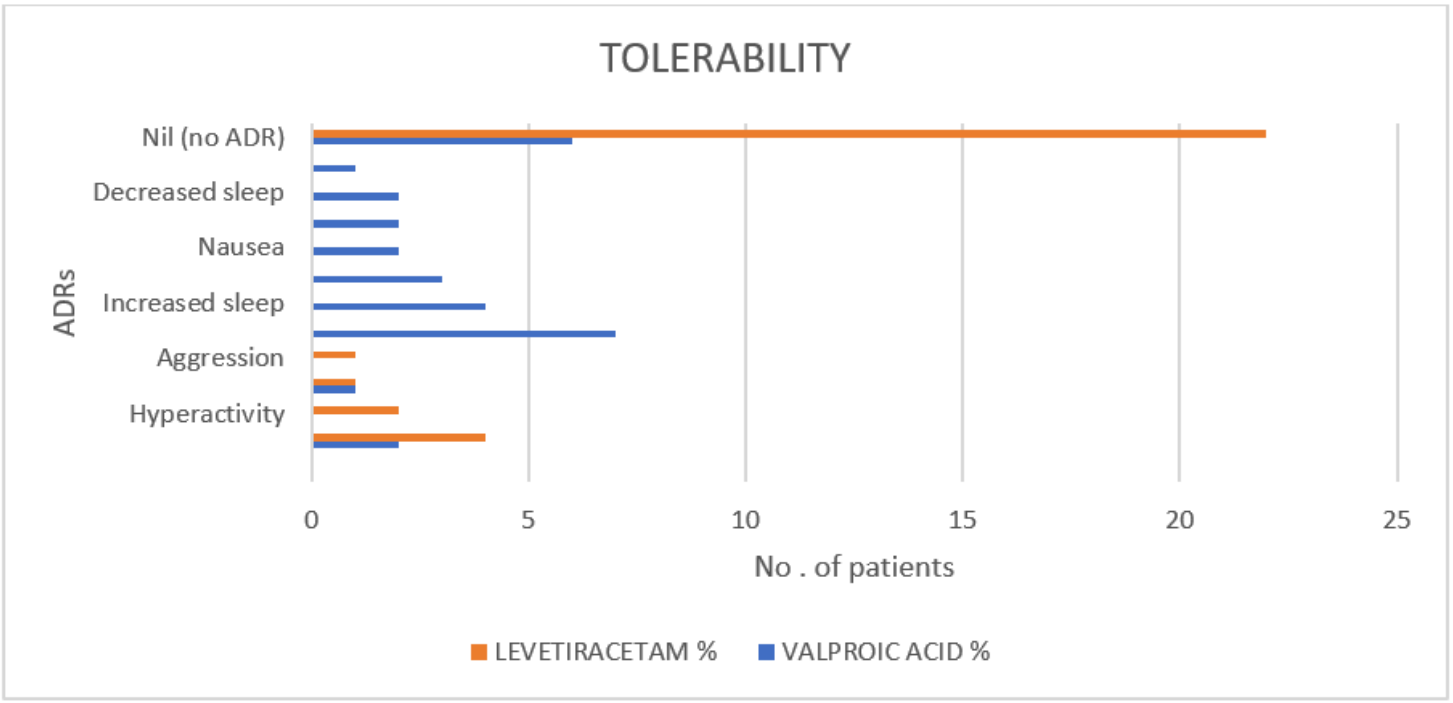


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