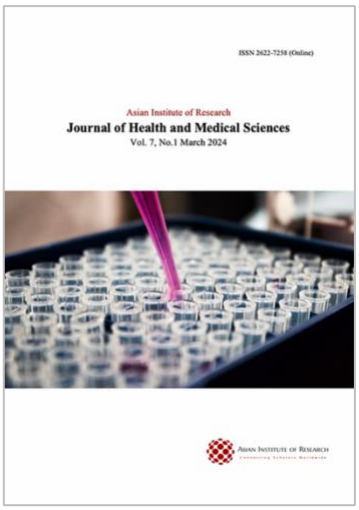

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Comparison Between Valproic Acid and Levetiracetam to Cognitive Function in Idiopathic Generalized Epilepsy

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Abstract
Epilepsy affects cognition through several mechanisms in a complex relationship. Valproic acid (VPA) and levetiracetam (LEV) are widely used due to their good efficacy and tolerability profiles. However, VPA may cause impairment of spatial working memory. There has not been much explanation regarding the negative cognitive side effects of LEV, few research suggests that LEV may even have a stimulating effect on cognition. Evidence of the comparative effects of anti-epileptic drugs on cognitive function is still limited. Objective: To investigate the effects of VPA monotherapy and LEV monotherapy on idiopathic generalized epilepsy patients. Methods: This was a cross-sectional observational study of patients with IGE taking either VPA monotherapy (n=28) or LEV (n=25). All patients underwent cognitive function assessment using MoCA-Ina, CDT, TMT A and B. Results: There was a significant association between 64.3% of patients taking VPA having MoCA-Ina score <26 vs. only 12% in patients taking LEV (OR 13.2, 95% CI 3.150-56.309, p<0.001), 35.7% of patients taking VPA vs. 0% in patients taking LEV on TMT-A score (p<0,001), and 46.4% of patients taking VPA vs. 4% in patients taking LEV on TMT-B score (OR 20.80, 95% CI 2.462-175.696, p 0,001). Neither patients with VPA monotherapy nor LEV monotherapy was statistically significant in CDT score (57.1% vs 36%, OR 0.422, 95% CI 0.139-1.277, p 0.170). Conclusion: This study showed patients with VPA have lower cognitive function than LEV. Further studies on cognitive function in epilepsy are recommended to provide information to assist in efficient drug selection decision-making for patients.

Keywords: Cognitive, Valproic Acid, Levetiracetam, Idiopathic Generalized Epilepsy

1. Introduction

Epilepsy is a neurological disease that is common in all age groups, races, social classes, and geographic locations. In developed countries, the annual incidence of epilepsy is estimated to be about 50 per 100,000 population and the prevalence is estimated to be about 700 per 100,000 population, the number is estimated to be higher in developing countries (Kusumastuti, 2019).

The goal of treating epilepsy with an anti-epileptic drug (AED) is to stop seizures without side effects that reduce the quality of life (Shih et al., 2013). AED is effective in reducing the risk of recurrent seizures, however, treatment does not alter the underlying disease and does not change the long-term prognosis. AED is associated with various side effects that should be considered during treatment. People with epilepsy are often affected by many other health problems. Seizures can cause morphological and functional changes in the brain, manifesting as cognitive and neuropsychological impairment. If epileptic seizures are not properly treated and controlled, they can lead to permanent cognitive dysfunction (Novak et al., 2022).

Cognitive impairment is a significant decline in the functioning of one or more domains of cognition (complex attention, executive function, learning, memory, language, perceptual-motor, or social cognition) from previous levels of performance (Asnakew et al., 2022; Aninditha, 2022). Difficulties with cognition are one of the most common problems that are more burdensome yet often overlooked. The most commonly reported cognitive problems associated with epilepsy are memory impairment, cognitive slowing, and attention deficits that negatively impact daily functioning, such as school work in children and driving ability in adults (Novak et al., 2022; Lodhi, 2012; Sayed et al., 2023).

Proper selection of AED can control epileptic seizures in almost 70% of epilepsy patients (Aninditha, 2022). Valproic acid is a widely used AED in both adults and children due to its good efficacy and tolerability profile with a broad spectrum of effectiveness for various seizures and epileptic syndromes (Romoli, 2019). However, it was found that clinically relevant doses of VPA can decrease spatial working memory (Pannangrong et al., 2019). Similar to valproic acid, levetiracetam (LEV) is widely used as it has a broad spectrum and has shown efficacy as monotherapy in patients newly initiated on the drug (El Sabaa et al., 2020). The consumption of valproate (VPA) and levetiracetam (LEV) has been reported to affect cognitive function, visuospatial memory to attention. The hippocampus plays an important role in learning, memory, and spatial navigation (Romoli et al., 2019; Pannangrong et al., 2019). Neuropsychological theories on hippocampal function have been related to inhibition, memory, and spatial function (Szabo, 2014). Neuropsychological assessment aims to assess the extent to which a particular skill is impaired and to determine the brain regions that may be damaged.

Although there are neuropsychological studies that have compared newer-generation drugs with older AEDs for high risk of cognitive impairment, the comparative effects of newer-generation drugs remain unclear (Khanna, 2019). However, evidence of the comparative effects of AED on cognitive function is still limited, while most recent studies have focused on comparing the efficacy and tolerability of AED (El Sabaa, 2020). Due to study limitations and the lack of research in Indonesia and specifically in Makassar that directly assesses this, a study was conducted to gain a better understanding of the comparative evaluation of valproic acid and levetiracetam as a single therapy for epilepsy on cognitive function. The main objective of this study was to determine the differences in cognition and memory tests through the MoCA-Ina, Clock Drawing Test (CDT), Trail Making Test (TMT) A and B questionnaires in the AED VPA and LEV groups.

2. Method

2.1 Research Design, Location and Time

This study was observational and cross-sectional study starting from August–December 2023. Subjects with epilepsy were recruited at Wahidin Sudirohusodo General Hospital Makassar, educational network hospitals, and private practices in Makassar, South Sulawesi, Indonesia.

2.2 Participant

Inclusion criteria are epilepsy patients who based on history, and/or EEG, have been diagnosed with idiopathic generalized epilepsy (IGE), are aged 12-60 years, can read and write, and consume AED monotherapy VPA for at least 6 months or LEV for at least 6 months. All of the patients provided their consent to participate in the research study. Exclusion criteria were IGE patients who changed AED more than twice, did not regularly control treatment, and had a history of stroke, brain infection, brain neoplasm, and moderate to severe head trauma.

2.3 Neuropsychological tests

Assessment of neuropsychological aspects consists of MoCA-Ina, Clock Drawing Test, and Trail Making Test A and B.

The Indonesian version of the MoCA test was used and validated in Indonesia for a population with cognitive impairment. MoCA-Ina evaluates cognitive domains such as memory, attention, concentration, executive functions, language, visuospatial abilities, capacity of abstraction, calculation, and orientation. The maximum score is 30, with a score below 26 suggesting cognitive impairment. In this study, the addition of 1 point was maintained for those patients with less than 12 years of schooling.

Clock Drawing Test (CDT) is a cognitive function instrument specifically for assessing visual memory and reconstruction, visuospatial skills, and executive function where the patient is asked to draw a clock showing a certain time. The normal score is 4, and further cognitive evaluation is needed if the score is <4.

Trail Making Test (TMT) is used to assess attention, executive and visuospatial skills, and psychomotor speed. The test consists of two parts (A and B). In the TMT-A test, subjects were asked to draw lines connecting 25 circles labeled with numbers; whereas in TMT-B, subjects were asked to alternately connect circles labeled with numbers and letters (1-A-2-B-3-C, etc.). The maximum time for TMT-A was 180 seconds, while TMT-B was 300 seconds.

2.3 Analyses

The research data was done using the SPSS version 27 program. Continuous variables were reported as medians (25th, 75th percentiles; IQR) for non-parametric data. The chi-squared and Mann–Whitney U tests were used to examine the differences between the VPA and LEV groups; a p-value < 0.05 was considered significant.

3. Results

3.1 Characteristics of the subjects

A total of 62 subjects were examined; of these, 3 did not meet the study criteria, and 6 refused to participate. The total sample analyzed was 53 subjects (Figure 1). Demographic characteristics based on age: the youngest age of epilepsy patients in this study was 12 years old, and the oldest was 57 years old, with a mean age of 23.75 ± 10.57 years. Based on gender, there were 24 male subjects (45.3%), while there were 29 female subjects (54.7%). The characteristics of the research subjects are summarised in Table 1.

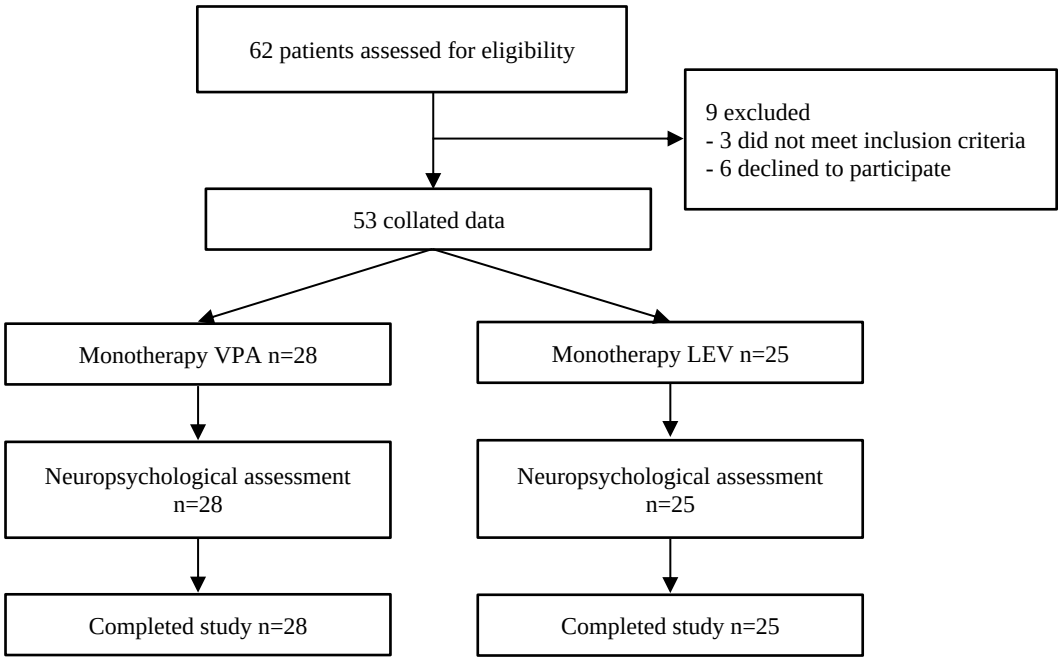

Figure 1: Patients' disposition study flow diagram

Table 1: Demographic profile and characteristics of patients in the VPA and LEV groups

Patient characteristics				
	Classification	**VPA (n=28)**	**LEV (n=25)**	**p-value**
Age (years)	12 – 16	8 (28,6%)	6 (24%)	0,162[a]
	17 – 30	14 (50%)	14 (56%)	
	31 – 45	6 (21,4%)	2 (8%)	
	> 45	0 (0%)	3 (12%)	
Sex	Male	17 (60,7%)	7 (28%)	0,035[a]
	Female	11 (39,3%)	18 (72%)	
Education level	Primary school	8 (28,6%)	4 (16%)	0,421[a]
	Middle school	5 (17,9%)	4 (16%)	
	Senior high school	11 (39,3%)	9 (36%)	
	High education	4 (14,3%)	8 (32%)	
Employment status	Employee	11 (39,3%)	4 (16%)	0,116[a]
	Unemployed	17 (60,7%)	21 (84%)	
History of illness	Febrile seizures	5 (17,9%)	9 (36%)	0,237[a]
	Mild head injury	3 (10,7%)	2 (8%)	1,000[a]
	Family history of epilepsy	1 (3,6%)	1 (4%)	1,000[a]
Type of IGE	GTCA	22 (78,6%)	18 (72%)	0,777[a]
	JME	2 (7,1%)	4 (16%)	
	CAE	1 (3,6%)	1 (4%)	
	JAE	3 (10,7%)	2 (8%)	

Values expressed in n (%)

[a]Chi-square test

3.2 MoCA-Ina test between the VPA group and LEV group

Table 2 presents the neuropsychological test results for the groups. This study found an association in the MoCA-Ina test where the cognitive function of the VPA group was significantly lower than that of the LEV group ($p<0.001$, 64.3% vs. 12%). Data is not normally distributed. Using the Mann-Whitney test, the median score in the VPA group was 25.00 (9.00-29.00), while the LEV group was 27.00 (23.00-30.00). On the MoCA-Ina domain, both groups showed indicators of cognitive impairment with worse performance on visuospatial ($p<0.05$), language ($p<0.01$), and delayed recall ($p=0.00$) task instruments as shown in Table 3.

Table 2: Cognitive performance in the VPA group and LEV group

Categories of differences in cognitive function							
		VPA (n=28)	**LEV (n=25)**	**Total**	**OR**	**CI 95%**	**p-value**
MoCA-Ina	**Normal**	10 (35,7)	22 (88)	32 (60,4)	13,2	3,150 – 56,309	0,000[a]
	Impaired	18 (64,3)	3 (12,0)	21 (39,6)			
CDT	**Normal**	12 (42,9)	16 (64)	28 (52,8)	0,422	0,139 – 1,277	0,170[a]
	Impaired	16 (57,1)	9 (36)	25 (47,2)			
TMT-A	**Normal**	18 (64,3)	25 (100)	43 (81,1)	-	-	0,000[a]
	Impaired	10 (35,7)	0 (0)	10 (18,9)			
TMT-B	**Normal**	15 (53,6)	24 (96)	39 (73,6)	20,80	2,462 – 175,696	0,001[a]
	Impaired	13 (46,4)	1 (4)	14 (26,4)			

[a]Chi-square test

Table 3: Cognitive domain scores in MoCA-Ina scores between VPA group and LEV group subjects

Parameter MoCA-Ina	**VPA**		**LEV**		**p-value**
	Min - max	**Median**	**Min - max**	**Median**	
Visuospatial	1,00 – 5,00	4,00	3,00 – 5,00	5,00	0,040[b]
Naming	1,00 – 3,00	3,00	2,00 – 3,00	3,00	0,075[b]
Attention	0,00 – 6,00	5,00	1,00 – 6,00	5,00	0,341[b]
Language	0,00 – 3,00	2,00	1,00 – 3,00	3,00	0,002[b]
Abstraction	0,00 – 2,00	1,00	0,00 – 2,00	1,00	0,852[b]
Delayed recall	2,00 – 5,00	4,00	2,00 – 5,00	5,00	0,000[b]
Orientation	2,00 – 6,00	6,00	5,00 – 6,00	6,00	0,609[b]
Total	9,00 – 29,00	25,00	23,00 – 30,00	27,00	0,001[b]

[b]Mann-Whitney test

3.3 CDT test between the VPA group and LEV group

The VPA and LEV groups did not have any significant differences in CDT scores (p-value of 0.170, p>0.05, 57.1% vs. 36%). Data is not normally distributed. According to the Mann-Whitney test, the median score for CDT in the VPA and LEV groups was 3.00 (0.00-4.00) compared to 4.00 (2.00-4.00).

3.4 TMT-A and TMT-B test between the VPA group and LEV group

In the TMT-A test, it was observed that the VPA group had a significantly lower level of cognition than the LEV group (p<0.001, 35.7% versus 0%). Data is not normally distributed in both TMT-A and TMT-B. The VPA and LEV groups had a median TMT-A score of 106.50 (30.00-243.00) and 82.00 (35.00-131.00) based on the Mann-Whitney test. The VPA group and the LEV had a significant difference in TMT-B scores (p = 0.001, 46.4% vs. 4%), as shown by similar results. The median scores for TMT-B in the VPA and LEV groups were 271.50 (48-643) versus 127.00 (55.00-347.00) using the Mann-Whitney test.

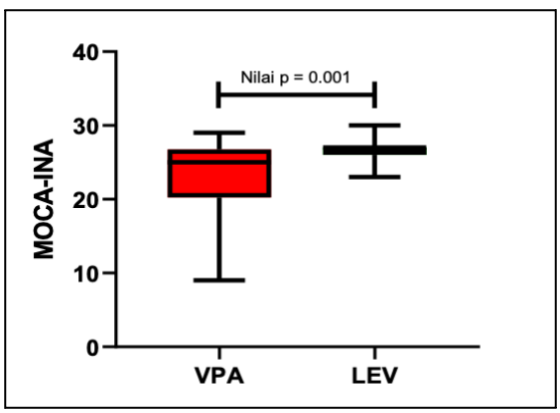

Figure 2: The median score of MoCA-Ina in the VPA group and LEV group

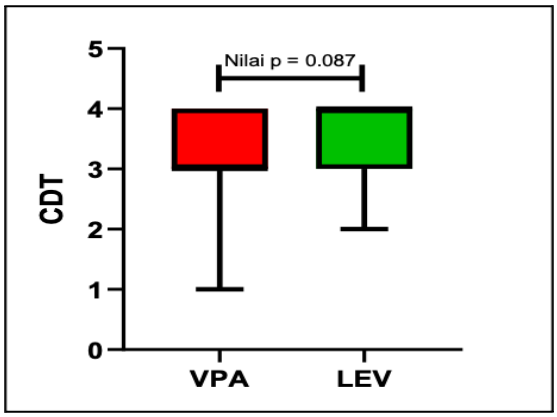

Figure 3: The median score of CDT in the VPA group and LEV group

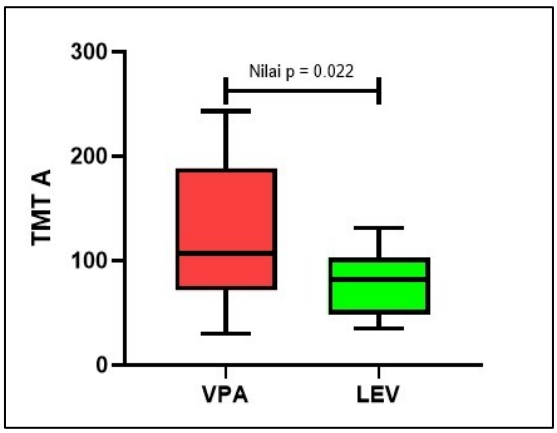

Figure 4: The median score of TMT-A in the VPA group and LEV group

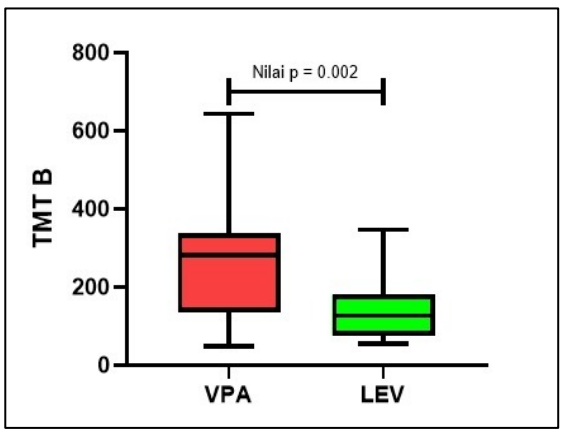

Figure 5: The median score of TMT-B in the VPA group and LEV group

4. Discussion

The study involved 28 subjects receiving VPA monotherapy treatment, and 25 patients receiving LEV monotherapy treatment. Several studies have demonstrated that the AED has negative effects on cognition (Novak et al., 2022; Lodhi, 2012). The age range in this study was between 12 and 57 years, with a mean age of 23.75 ± 10.57 years. The male-to-female ratio was 24:29, with a significant difference between the two (p 0.035). The use of age- and sex-corrected normative data prevented further analysis controlling for this difference. The two groups had no differences in education (p = 0.421).

The median MoCA-Ina score was 25.00 (9.00-29.00) in the VPA group and 27.00 (23.00-30.00) in the LEV group. In our study, 21 patients scored below the limit set in the MoCA-Ina questionnaire, of which 18 subjects (64.3%) were found to be impaired in the VPA group. Similar to previous studies, the use of VPA results in a decrease in MoCA-Ina scores. Romoli (2019) mentioned in animal studies that used location tests to evaluate spatial memory, there was a relationship between VPA and cognitive deficits thought to be caused by the suppression of hippocampal neurogenesis. In contrast to VPA, levetiracetam has had significant positive effects on the cognitive profile of epilepsy patients in different studies (Khanna, 2019; El Sabaa, 2020; Koo et al., 2013). According to this study, MoCA-Ina scores decreased by 12.0% for three people in the LEV group. In a randomized clinical trial, LEV was well tolerated and improved the performance of spatial memory and executive function tasks in patients with Alzheimer's disease and epileptiform activity (Vossel et al., 2021). In this study, cognitive impairment was reported mainly due to the use of VPA on several analyzed MoCA-Ina parameters. The domains of impairment were visuospatial (p 0.04), language (p 0.002), and delayed recall (p 0.00). Other findings in a cross-sectional study by Harahap (2022) of 155 patients with epilepsy, were reported similarly in our study with impaired cognitive impairment in several MoCA-Ina domains such as visuospatial and executive function, naming, attention, language, abstraction, delayed recall and orientation ($p<0.001$). While MoCA-Ina domain scores cannot fully replace neuropsychological tests, they can complement MoCA-Ina total scores in the systematic assessment of early neurocognitive disorders. This can help to conserve the use of neuropsychological tests for patients who are more likely to require further assessments.

A total of 25 subjects (47.2%) with CDT < 4 results requiring further cognitive evaluation with VPA group subjects was found to be more at 16 people (57.1%) than the LEV group 9 people (36%). Comparison of VPA and LEV groups was found to be not meaningful to CDT in this study ($p = 0.170$). Claudya (2018) with a similar study conducted a study with AED monotherapy carbamazepine and phenytoin the results there was no significant difference between the two groups. A case-control involving 80 epilepsy patients also reported no significant difference in the CDT examination ($p=0.060$) (Njamnshi et al., 2020). A control sample study involving 371 subjects reported a significant correlation between CDT and epilepsy duration (p 0.013) (Tedrus et al., 2020). Furthermore, a study by Yaksa (2018) showed a significant difference between CDT with the onset of seizure ($p < 0.05$). While the CDT scoring methods are valuable for their objectivity and ease of use, they cannot often assess specific characteristics of neurocognitive disorders in each phase of the task. This limits their usefulness in analyzing performance data.

In the TMT-A test, the mean value was 106.50 (30.00 - 243.00) in the VPA group and 82.00 (35.00 - 131.00) in the LEV group where there was a significant difference between the two ($p < 0.05$). Furthermore, the TMT-B test results with a mean value of 281.50 (48.00 - 643.00) in the VPA group and 127.00 (55.00 - 347.00) in the LEV group with a significant difference between the two groups (p 0.002). A previous study has shown the length of seizure duration was associated with poor TMT-B performance, and the use of AED polytherapy was associated with worse TMT-A outcomes (Hasegawa, 2023). Liu et al. (2016) associated interictal epileptiform discharges (IEDs) affecting cognitive performance with TMT-B outcome ($p=0.012$). The study by Hasegawa (2022) also revealed that minimal AED use and a higher education level were associated with a shorter time to complete TMT-A and TMT-B. This study supports the results of impaired executive function in this study.

There was a difference in significance between the CDT and TMT examinations (TMT-A and TMT-B), where the TMT results showed a significant difference between the VPA and LEV groups, while the CDT had no significant difference between the two groups. It should be noted that most neuropsychological tests do not only assess one particular domain or skill component. CDT is a brief test that permits the exploration of a wide range of cognitive processes including attention, understanding of instructions, planning, visuospatial ability, visual construction, programming and graphomotor performance, numerical knowledge, abstract thinking, symbolic representation, and semantic memory (Aguilar-Navarro et al., 2018). On the other hand, the TMT-A test results are related to cognitive domains such as visual scanning, attention, and processing speed, while TMT-B results are associated with more complex cognitive abilities, including working memory, complex set maintenance, switching, and mental flexibility (Du et al., 2022; Fellows et al., 2017). Similarly, hippocampal dysfunction does not cause a single deficit. The identification and quantification of cognitive function deficits obtained from

neuropsychological tests further enable the specification of dysfunctional processes that are characteristic of a particular disorder (Szabo, 2014).

Many other factors potentially contributing to cognitive dysfunction have been described, including age, disease duration, etiology, frequency of awakenings, and psychiatric disorders, but AED has been the focus of increased research attention as it represents a potentially modifiable risk factor (Novak et al., 2022; Njamnshi et al., 2022; Tedrus et al., 2020; Khalife et al., 2022). Along with the facilitation of the mitogen-activated protein kinase pathway, VPA modulates neurogenesis and blocks cognitive decline-induced hippocampal seizure activity (Romoli, 2019). It has been observed that VPA can lead to a reduction in spatial working memory. This effect is associated with a decrease in cell division required for neurogenesis in the hippocampus. The hippocampus is a crucial structure for spatial working memory and recognition that emerges as a main site of VPA action in causing cognitive decline (Pannangrong et al., 2019). Although some studies have shown a decrease in cognitive performance with VPA, other studies have reported that LEV has a favorable effect on cognition in attention, memory, and executive function (El Sabaa et al., 2020; Perkins et al., 2023). LEV reverses cognitive decline, behavioral abnormalities, hippocampal remodeling, and synaptic dysfunction (Sanchez et al., 2012). LEV is suggested to improve cognitive function, enhance cholinergic function, and prevent the formation of inflammation in neurons, neuronal apoptosis processes, and oxidative vulnerability. Administration of LEV can ameliorate the degeneration of cholinergic neurons due to inflammatory processes and oxidative vulnerability that can lead to several dysfunctions including impaired learning, memory, and attention (Mani, 2023). Data regarding AED-related cognitive dysfunction are widely reported involving the control of other confounding factors; however, cognition-related relationships are complex, and the contribution of AED cannot be easily separated from other factors (Foster et al., 2020). Thus, the outcomes of this research may not reflect or easily apply to actual clinical practice.

Enhancing the diagnosis and treatment, especially of elderly epilepsy patients requires a comprehensive understanding of cognitive decline and its associated risk factors (Miller et al., 2016). This study demonstrates the importance of early screening for cognitive impairment in epilepsy patients which should be done in conjunction with follow-up treatment, and this will improve the overall quality of life of epilepsy patients.

This study has several limitations. Firstly, the type of IGE, disease duration, length of AED consumption, and controlled seizures were not further differentiated. The data in this study may not be sufficient to determine certain effects that change over time. However, the design of this study provided an assessment of the effects of VPA and LEV monotherapy on cognitive function in IGE patients. Secondly, it should be noted that this study was not conducted as a randomized controlled trial. Thirdly, testing was done only once, although we applied advanced statistical methodology to look at confounding factors, which may have biased the results.

In conclusion, we have demonstrated that patients administered VPA exhibited lower cognitive function than those given LEV. Further research is recommended to provide information to assist in efficient drug selection decision-making for patients.

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Ethics Commission at the Faculty of Medicine, Hasanuddin University Makassar with No. 735/UN4.6.4.5.31/PP36/2023.

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Appendix A

The mean, SD, median, and range score of VPA group and LEV group to Neuropsychological tests

Group	VPA					LEV					p-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
MoCA-Ina	23,50	4,44	25,00	9,00	29,00	26,80	1,61	27,00	23,00	30,00	0,001*
Visuospatial	3,79	1,20	4,00	1,00	5,00	4,44	0,65	5,00	3,00	5,00	0,040*
Naming	2,50	0,75	3,00	1,00	3,00	2,84	0,37	3,00	2,00	3,00	0,075
Attention	4,32	1,59	5,00	0,00	6,00	4,80	1,12	5,00	1,00	6,00	0,341
Language	1,71	1,12	2,00	0,00	3,00	2,60	0,58	3,00	1,00	3,00	0,002*
Abstraction	0,96	0,69	1,00	0,00	2,00	1,00	0,71	1,00	0,00	2,00	0,852
Delayed recall	3,61	1,07	4,00	2,00	5,00	4,56	0,87	5,00	2,00	5,00	0,000*
Orientation	5,82	0,77	6,00	2,00	6,00	5,96	0,20	6,00	5,00	6,00	0,609
TMT-A	126,11	65,93	106,50	30,00	243,00	79,24	30,61	82,00	35,00	131,00	0,022*
TMT-B	256,18	142,02	281,50	48,00	643,00	135,88	66,81	127,00	55,00	347,00	0,002*
CDT	3,14	0,93	3,00	1,00	4,00	3,56	0,65	4,00	2,00	4,00	0,087

SD: standard deviation

Mann-Whitney test