

Effects of Levetiracetam Compared to Valproate on Cognitive Functions of Patients with Epilepsy

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Objective: This study compared the effect of levetiracetam (LEV) as monotherapy to sodium valproate (VPA) as monotherapy on cognitive functions in patients with epilepsy.

Methods: This was a comparative prospective study on 50 patients with newly diagnosed epilepsy started on antiseizure medications. Patients were selected from the neurology-outpatient clinics at Minia University Hospital, Minia, Egypt. They were divided into two groups: group treated with LEV and group treated with VPA. All patients were subjected to cognitive function assessment using reaction-time tests, trail-making tests, and Wisconsin card-sorting test before treatment and 3 months after treatment.

Results: Both groups of patients showed reduction in seizure frequency. However, patients on LEV showed significant improvement in measured cognitive functions 3 months after starting treatment, while patients in the VPA group showed significant impairment in measured cognitive functions 3 months after starting treatment.

Conclusion: Both groups of patients showed reduction in seizure frequency. However, patients on LEV showed significant improvement in measured cognitive functions 3 months after starting treatment, while patients in the VPA group showed significant impairment in measured cognitive functions 3 months after starting treatment.

Keywords: cognitive function, epilepsy, levetiracetam, valproate, monotherapy

Introduction

Epilepsy is the most common neurological disease. According to the World Health Organization (WHO), 50 million people are suffering from epilepsy.¹ Antiseizure medications are the backbone of epilepsy management for patients of all ages. The target of treating epileptic patients is to control seizures completely without causing unwanted side effects.² Antiseizure medications are known to affect the cognitive abilities in epileptic patients. Slowing of mental function and decreased concentration, awareness, and psychomotor speed are the main adverse cognitive events related to antiseizure medications.³ Antiseizure medications affect cognition by reducing neuron excitability or enhancing inhibitory neurotransmission.⁴ The presence of cognitive side effects caused by antiseizure medications is a major concern for patients with epilepsy taking medication.⁵

Levetiracetam (LEV), one of the most prescribed antiseizure medications, is widely used in many forms of treatment for epilepsy. It is used in the treatment of focal-onset, myoclonic, and generalized tonic-clonic seizures as monotherapy and add-on therapy.⁶ LEV shows good tolerability and a positive impact on neuropsychological tests. Many studies have shown that no significant changes are observed in cognitive function with LEV.⁷ Sodium valproate (VPA) is also a broad-spectrum

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antiseizure medication used not only for epilepsy but also for other neuropsychiatric disorders, such as bipolar disease and migraine. It has been associated with some cognitive impairment in bipolar disease.⁸ There is limited evidence on the comparative effects of antiseizure medications on cognitive functions, while most recent studies have focused on comparisons of efficacy and tolerability of antiseizure medications.^{9,10} This study was performed to compare the effects of two well-known antiseizure medications LEV and VPA as monotherapy on cognitive functions of patients with epilepsy.

Methods

Subjects

This was a comparative prospective open study undertaken at neurology-outpatient clinics of Minia University Hospital, Minia, Egypt from January 2018 to March 2019. Fifty patients with newly diagnosed epilepsy were included after obtaining written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the Commission on the Ethics of Scientific Research, Faculty of Pharmacy, Minia University.

Subjects were divided into two groups of 25 each. The first group was treated with LEV, and the second group treated with VPA, both as monotherapy, based on physician discretion. Inclusion criteria were newly diagnosed focal and generalized epilepsy patients according to classification of epileptic seizures proposed by the International League Against Epilepsy, age ≥ 16 years, not on antiseizure medication, having been prescribed monotherapy with one of the two antiseizure medications (LEV and VPA).

Exclusion Criteria

Patients with any progressive central nervous system disease, extreme cardiovascular abnormality, underlying malignancy and hypersensitivity to any of the medications tested, untreated serious concurrent disease, irregular liver and kidney function, pregnant and lactating, and a history of drug-related seizures, alcohol, or acute medical or psychiatric conditions were excluded from the analysis.

Procedure

A detailed history and general physical and neurological examinations were performed for each patient. Seizures were classified according to the International League Against Epilepsy 2017 classification of seizures.¹¹

Electroencephalography was done for confirmation of seizure type. Dose ranges at the start of the study were 1,000–2,000 mg/day for LEV and 1,000–1,500 mg/day for VPA. Follow up duration was 3 months.

Cognitive Function Tests

Assessment of cognitive function was based on the simple reaction–time test, choice reaction–time test, trail-making tests A and B, and Wisconsin card-sorting test (WCST). Patients were evaluated before treatment and 3 months after treatment.

Simple and Choice Reaction–Time Tests

The basic idea is that response times represent the time it takes to perceive a stimulus, acquire memory information, and activate a muscle response. Therefore, response times can be used to find out how long basic thought processes take. The test score is the reaction time in milliseconds. For the simple reaction–time test, there is only one stimulus, and the subject needs to respond each time it occurs. In this task, the participant needs to wait until they see a black cross on the white square. When that happens, they press the space bar. As such, there is one stimulus (black cross) and one response (pressing the space bar). For the choice reaction–time test, there are several stimuli and each stimulus needs a different response. In this task, the participant needs to wait until they see a black cross on one of the four white squares (eg, there are four black-cross positions, which counts as four different stimuli). When that happens, they will press on the corresponding key (z, x, c, or b). As such, there are four stimulus–response associations.¹²

Trail-Making Tests

These are visual-focus and task-changing neuropsychological tests. They can provide data on the speed of visual search, scanning, processing speed, mental flexibility, and executive functioning. Tasks require a subject to attach a series of consecutive goals on a sheet of paper or computer screen. The score of the test is the number of seconds needed to complete the mission.¹³ There are two parts to the test:

Trail-making part A : all numbers (1, 2, 3, etc) are goals and must be linked in sequential order by the subject. This method is specifically used to examine the speed of cognitive processing

Trail-making part B : the topic alternates between numbers and letters (1, A, 2, B, etc). This method is used to evaluate the functioning of the executive.

Wisconsin Card-Sorting Test

This is a test of attention, concentration, and problem-solving. In the WCST, cards must be graded according to different criteria by individuals. Every card is categorized in four ways, and the only input is whether the classification is right or not. Cards can be categorized by the color of their symbols, the form of the symbols, or the number of symbols on each card. The classification rule changes every ten cards, and this ensures that once the participant has decided the rule, one or more mistakes will be made by the participant when the rule changes. The task measures how well people can adapt to the changing rules. The test score is the number of correct cards and the number of perseverative and non-perseverative errors.¹⁴

Statistical Analysis

Results are expressed as means \pm SE. Differences among groups were statistically analyzed by one-way ANOVA, followed by Tukey's HSD post hoc test for multiple compar-

isons for all tests $P < 0.05$ was considered statistically significant. All data analyses were performed using GraphPad Prism 7.

Results

Demographic Profile of Patients

Fifty patients who fulfilled the eligibility criteria were enrolled, as shown in Figure 1. Demographic data are shown in Table 1. No significant differences were observed between the groups.

Seizure Frequency Between LEV Group and VPA Group

Patients treated with LEV reported lower seizure frequency at 3 months after treatment (mean reduction from pretreatment was 6.76 ± 4.4 to 0.17 ± 0.49 at 3 months after treatment). In the VPA group, mean reduction from pretreatment was 6.88 ± 4.3 to 0.23 ± 0.52 at 3 months after treatment. However, this difference was not statistically significant. Both drugs as monotherapy showed similar seizure-frequency reduction (Table 2).

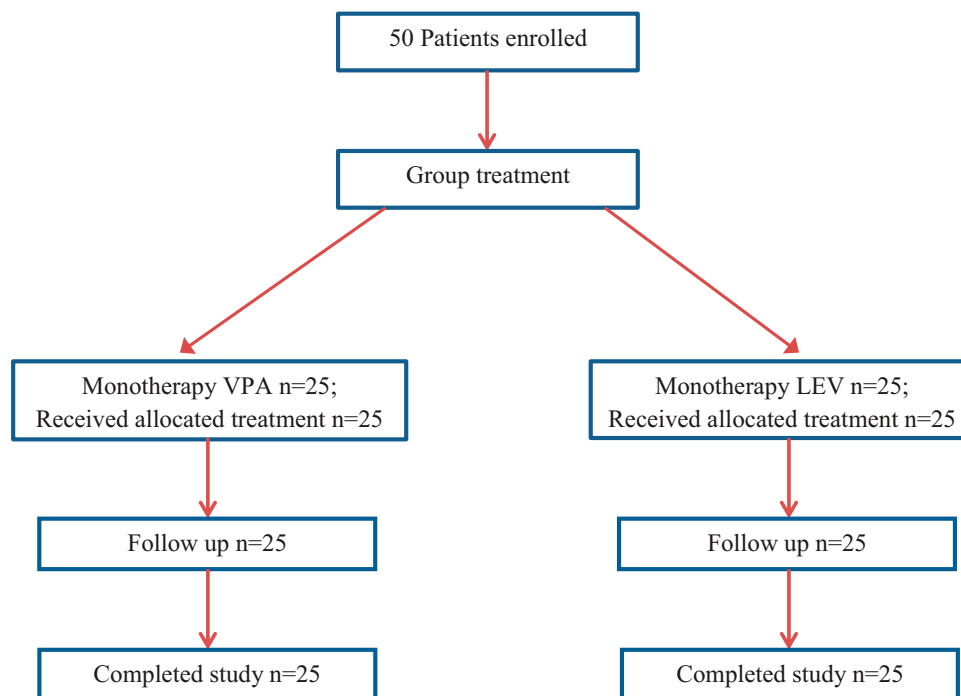


Figure 1 Flow chart for patient disposition.

Abbreviations: LEV, levetiracetam, VPA, sodium valproate.

Table 1 Demographic Profile of Patients of Epilepsy in Both Groups

Demographic Profile	LEV Group (n= 25)	VPA Group (n= 25)	P-value
Age (mean±SD)	39.76±12.7	38.44±12.5	0.7
Sex			
Males	13 (52.0%)	16 (64.0%)	0.5
Females	12 (48.0%)	9 (36.0%)	
Educational level			
Primary School	9 (36.0%)	8 (32.0%)	0.9
Secondary School	16 (64.0%)	17 (68.0%)	
Types of seizures			
Generalized tonic clonic seizures	22 (88%)	19 (76.0%)	0.4
Focal Motor seizures	3 (12.0%)	6 (24.0%)	

Table 2 Comparison of the Seizure Frequency Between LEV Group and VPA Group

Seizures/Month	LEV (Mean ±SD) (n=25)	VPA (Mean ±SD) (n=25)	P-value
Before treatment	6.76 ±4.4	6.88±4.3	0.9
One month after treatment	3.68 ±4.0	4.36±4.2	0.5
Two months after treatment	0.95 ±1.33	2.16±3.4	0.1
Three months after treatment	0.17 ± 0.49	0.23±0.52	0.7

Table 3 Comparison of the Seizure Freedom Between LEV Group and VPA Group

Seizure Freedom	LEV (Mean ±SD) (n=25)	VPA (Mean ±SD) (n=25)	P-value
One month after treatment	5 (20%)	4 (16%)	0.9
Two months after treatment	14 (56%)	10 (40%)	0.5
Three months after treatment	20 (80%)	18 (72%)	0.6

Seizure Freedom Between LEV Group and VPA Group

Patients in the LEV group achieved better seizure control than the VPA group: seizure freedom was 80% at 3 months after treatment for the LEV group and 72% for the VPA group. However, this difference was not statistically significant (Table 3).

Cognitive Function Tests

Simple Reaction–Time Test

Comparison of simple reaction–time test-score changes between groups revealed there was deterioration in scores in the VPA group compared to scores in the LEV group, which showed improvements in scores. There was a significant difference between groups 3 months after treatment, where means were 592.7±238.3 for LEV and 927.1±322.2 for VPA ($p=0.005$). A significant improvement was seen from 861.2±317.8 at pretreatment to 592.7±238.3 at 3 months after treatment in the LEV group ($p=0.03$). In the VPA group, scores deteriorated from 713.4±282.2 at pretreatment to 927.1±322.2 at 3 months after treatment, which was not statistically significant ($p=0.1$) (Figure 2).

Choice Reaction–Time Test

Comparison of choice reaction–time test-score changes between groups revealed deterioration in the scores in the VPA group compared to scores in the LEV group, which showed improvements. There was a significant difference between groups 3 months after treatment, with means of 895.5±238.1 for LEV and 1501.3±296.3 for VPA ($p<0.0001$), and significant improvement was seen from 1267.5±327.4 at pretreatment to 895.5±238.1 at 3 months after treatment in the LEV group ($p=0.0003$). In the VPA group, mean scores deteriorated from 1240.0±294.6 at pretreatment to 1501.3±296.3 at 3 months after

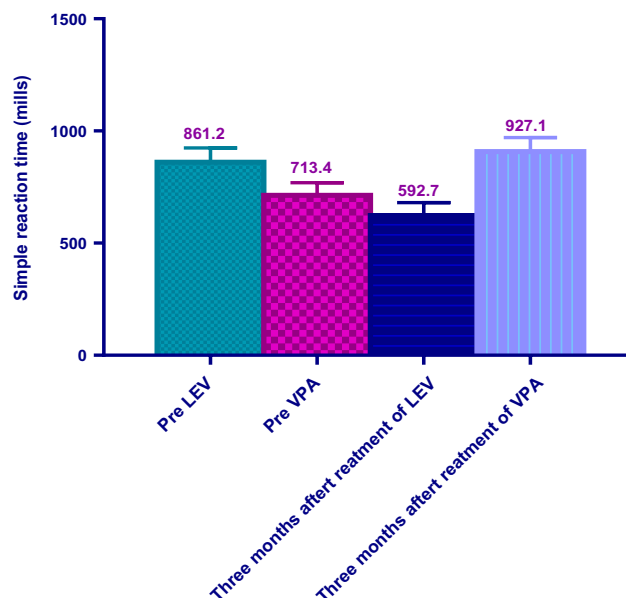


Figure 2 Effect of LEV group and VPA group on simple reaction time. **Abbreviations:** LEV, levetiracetam, VPA, sodium valproate.

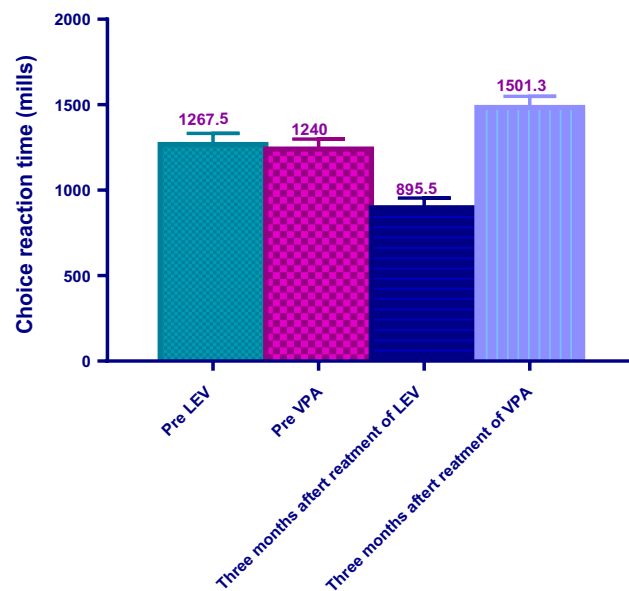


Figure 3 Effect of LEV group and VPA group on choice reaction time. **Abbreviations:** LEV, levetiracetam, VPA, sodium valproate.

treatment, which was also statistically significant ($p=0.03$) (Figure 3).

Trail-Making Test A

Comparison of trail-making test A–score changes between groups revealed there was deterioration in scores in patients of group VPA compared to patients of group LEV, which showed improvement. There was a significant difference between groups 3 months after treatment, with means of

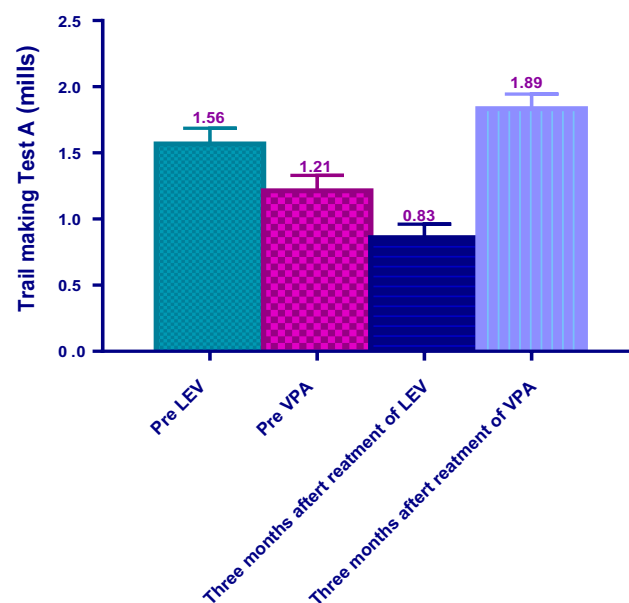


Figure 4 Effect of LEV group and VPA group on Trial making test A. **Abbreviations:** LEV, levetiracetam, VPA, sodium valproate.

0.83 ± 0.49 for LEV and 1.89 ± 0.62 for VPA ($p<0.0001$), and significant improvement was seen from 1.56 ± 0.59 at pre-treatment to 0.83 ± 0.49 at 3 months after treatment in the LEV group ($p=0.0001$). In the VPA group, scores deteriorated from 1.21 ± 0.58 at pretreatment to 1.89 ± 0.62 at 3 months after treatment, which was also statistically significant ($p=0.001$) (Figure 4).

Trail-Making Test B

Comparison of trail-making test B–score changes between groups revealed there was deterioration in scores in patients of group VPA compared to group LEV, which showed improvements. There was a significant difference between groups 3 months after treatment, where means were 1.63 ± 0.69 for LEV and 2.94 ± 0.84 for VPA ($p<0.0001$), and significant improvement from 2.45 ± 0.96 at pretreatment to 1.63 ± 0.69 at 3 months after treatment in the LEV group ($p=0.009$). In the VPA group, the score deteriorated from 2.05 ± 0.75 at pretreatment to 2.94 ± 0.84 at 3 months after treatment, which was also statistically significant ($p=0.003$) (Figure 5).

Wisconsin Card-Sorting Test

Comparison of WCST score changes in between groups revealed there was deterioration in WCST scores in patients of group VPA compared to group LEV, which showed improvements in scores. At 3 months after treatment, means were 44.04 ± 4.7 for LEV and 25.08 ± 5.33 for VPA ($p<0.0001$), and significant improvement

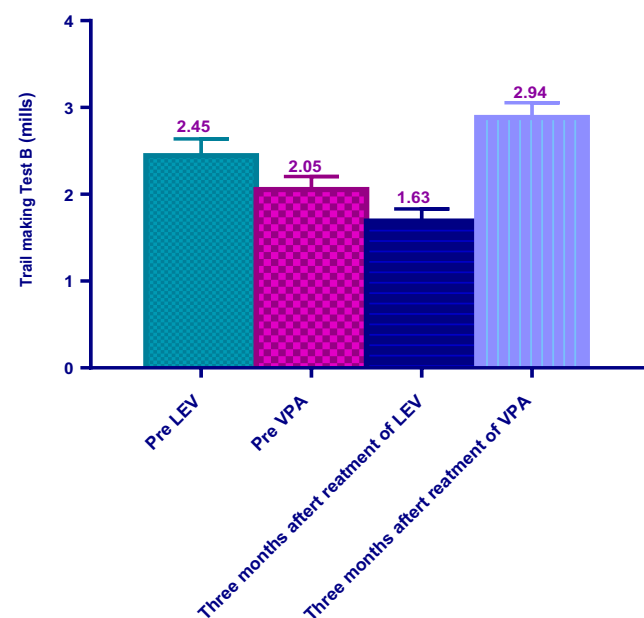


Figure 5 Effect of LEV group and VPA group on Trial making test B. **Abbreviations:** LEV, levetiracetam, VPA, sodium valproate.

was seen from 32.68 ± 5.8 pretreatment to 44.04 ± 4.7 at 3 months after treatment in the LEV group ($p < 0.0001$). In the VPA group, scores deteriorated from 33.2 ± 5.7 at pretreatment to 25.08 ± 5.33 at 3 months after treatment, which was also statistically significant ($p < 0.0001$). There was a significant difference in nonperseveration errors between groups 3 months after treatment, with means of 6.88 ± 2.7 for LEV and 14.36 ± 4.4 for VPA

($p < 0.0001$). A significant improvement was seen from 12.76 ± 3.8 at pretreatment to 6.88 ± 2.7 at 3 months after treatment in the LEV group ($p < 0.0001$). In the VPA group, scores deteriorated from 11.76 ± 4.2 at pretreatment to 14.36 ± 4.4 at 3 months after treatment, which was not statistically significant ($p = 0.09$). There was a significant difference in perseveration errors between groups 3 months after treatment, with means of 9.08 ± 3.5

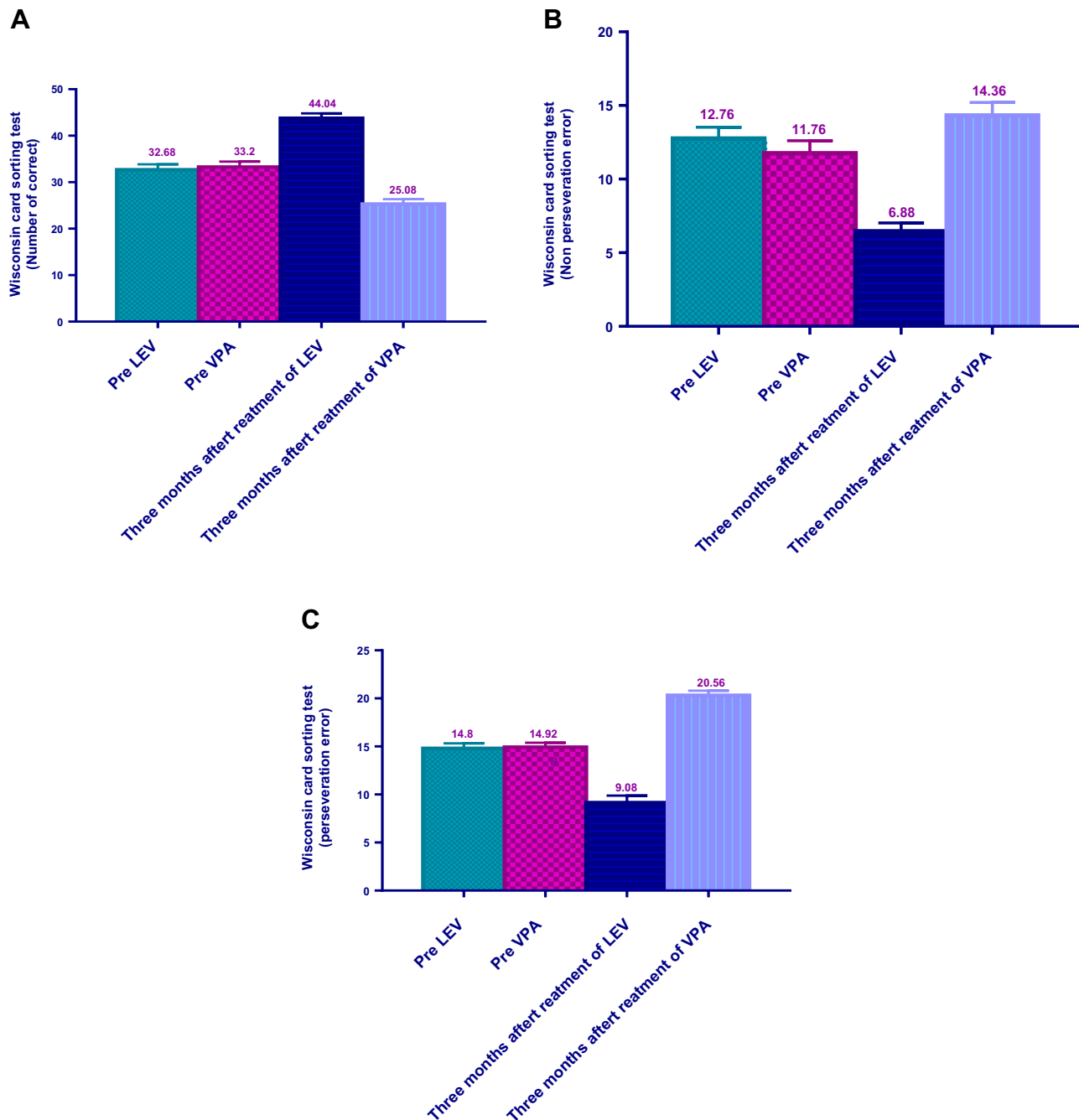


Figure 6 Effect of LEV group and VPA group on Wisconsin card sorting test (A) (Number of correct) (B) (Non-perseveration error) (C) (Perseveration error). **Abbreviations:** LEV, levetiracetam; VPA, sodium valproate.

for LEV and 20.56 ± 2.4 For VPA ($p < 0.0001$). Significant improvement was seen from 14.80 ± 2.6 at pretreatment to 9.08 ± 3.5 at 3 months after treatment in the LEV group ($p < 0.0001$). In the VPA group, scores deteriorated from 14.92 ± 2.3 at pretreatment to 20.56 ± 2.4 at 3 months after treatment, which was also statistically significant ($p < 0.0001$) (Figure 6).

Discussion

Epilepsy is generated by widespread and systematic mechanisms within the cerebral cortex, and memory and psychomotor functions may be impaired. Cognitive impairment can be due to the disease itself, as well as the antiseizure medications used in treatment. The effect of epilepsy itself on cognitive functions was not expected in our patients, as they were newly diagnosed cases. This study was designed to compare the effect of LEV to VPA on cognitive functions of patients with epilepsy when used as monotherapy. The authors of this study expected that LEV would have a good impact on cognitive functions compared to VPA.

General demographic features included in this analysis were age, sex, and educational level, and there were no statistically significant differences between the two groups treated with LEV and VPA. Better seizure-frequency reduction in patients treated with LEV and VPA as monotherapy was noted, in agreement with Ansa et al, who reported that VPA and LEV treatment caused undeniable reductions in seizure frequency before and after treatment.¹⁵ Along the same lines, our results showed improvements in mental skill domains following LEV monotherapy. This is consistent with previous studies that have found LEV as adjunctive treatment can reduce the frequency of seizures and enhance cognitive function.^{16,17}

The current results showed improvement in cognitive functions, including psychomotor speed, attention, mental flexibility, and executive function in the LEV group. This is in agreement with previous studies that have reported improvement in cognitive functions in patients treated with LEV as monotherapy.^{18,19} In the current study, it was found that there were highly significant improvements in attention and concentration measured by the WCST in the LEV group, in agreement with Noh et al, who found improvement in domains of cognition in patients treated with LEV as monotherapy.²⁰ Furthermore, that a highly significant improvements in processing speed, mental flexibility, and executive functioning on trail-making tests

A and B in the LEV group compared to the VPA group were demonstrated, in agreement with previous studies^{21,22} finding that both trail-making test A and reaction-time results showed significant differences with LEV treatment.

Similarly, previous reports have confirmed that there is no increase in reaction time and little evidence of attention impairment with new antiseizure medications compared to VPA.^{23,24} Possible mechanisms that might explain cognitive enhancement with LEV include the fact that LEV has a specific stereoselective binding site in the central nervous system at SV2A and that LEV can reduce neuronal necrosis and maintain long-term potentiation in the hippocampus, which may also contribute to its effects on cognition.²⁵ It has been suggested that LEV can improve attention and memory, because this compound is the α -ethyl analogue of the nootropic agent piracetam. Both belong to the pyrrolidine class, and these drugs might improve mental function, such as learning and memory, while protecting against seizures.²⁶ However, it is rational to suppose that improved cognitive function with LEV is due to its effect on the metabolism of some frontal areas.²⁷ Unfortunately, treatment with VPA caused an impairment in measured domains of cognitive performance. This is in agreement with a previous study, which reported that the choice reaction-time test showed an improvements in reaction time for some antiseizure medications and slowing for VPA.²⁸

On the other hand, in the current study patients who were treated with VPA had poor psychomotor skills and memory compared to those on LEV. Cavanna et al reported that VPA also impairs concentration, complex decision-making, and vasomotor function.²⁹ It was concluded that antiseizure medications, ie, phenytoin, VP, and carbamazepine, together with other drugs used in combination, have an effect on vision, awareness, comprehension, cognitive integration, and memory. The impact was more with polytherapy than monotherapy.³⁰ Also, it has been found that VPA is more likely to cause attentional dysfunction than ethosuximide in children with generalized absence seizures.³¹ In a previous study, it was noticed that in the elderly, VPA may occasionally cause cognitive impairment and that this may be reversible after VPA discontinuation.³² Recently, Khanna et al reported on cognitive impairment with VPA use in many parameters of cognition, whereas improvements in cognition were seen with LEV on the same parameters.³³

Limitations and Conclusion

The limitations of the present study were the limited sample size and limited follow-up. Longer follow-up would provide interesting information regarding the long-term effects of treatment, and may help in decision-making when choosing efficient drugs for patients. The findings from this study demonstrated obvious effects of antiseizure medications as monotherapy on neuropsychological measures of attention and memory, as the results of the current study established that the new-generation LEV can improve cognitive functions, in contrast to the older drugs VPA. In light of the current results, it can be concluded that using LEV a monotherapy in patients with epilepsy was effective in controlling seizures, with the additional benefit of improving cognitive functions.

Disclosure

The authors declare that there is no conflict of interest associated with this study.

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