



# EFFECT OF ANTIEPILEPTIC DRUGS ON P300 EVENT-RELATED POTENTIALS IN PATIENTS WITH EPILEPSY

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**SUMMARY** – Epilepsy is one of the most prevalent chronic neurological diseases, affecting about 70 million people worldwide. Patients with epilepsy often encounter cognitive dysfunction, which is influenced by different factors including age at the onset of epilepsy, etiology of epilepsy, type of seizures, seizure frequency and duration, psychiatric comorbidity, and antiepileptic drug (AED) therapy. Event-related potentials are useful, noninvasive, objective clinical and research instrument for evaluation of cognitive functions in patients. The aim of this study was to investigate and determine the effect of AED monotherapy and polytherapy on cognitive changes in patients with epilepsy, detected with P300 event-related potentials and compared with age- and gender-matched healthy individuals. The study was conducted in 82 patients with generalized and focal epilepsy and 82 healthy individuals aged 18–65 years. Cognitive evoked P300 potentials were recorded in all study subjects using auditory 'oddball' paradigm. The results showed the patients taking AED polytherapy to have a significantly longer P300 latency and significantly lower N200–P300 amplitude. These results indicate that AED polytherapy might worsen cognitive impairment in patients with epilepsy.

**Key words:** *Antiepileptic drugs; Epilepsy; P300 event-related potentials; Cognitive impairment*

## Introduction

Epilepsy is one of the most common neurological diseases characterized by an enduring predisposition to generate epileptic seizures<sup>1</sup>. Epilepsy affects more than 70 million people worldwide<sup>2</sup>. The incidence of epilepsy is 61.4 *per* 100 000 person-years<sup>3</sup>. The lifetime prevalence of epilepsy according to Fiest *et al.* is 7.6 *per* 1000 persons<sup>3</sup>. It has been observed that epilepsy can be associated with different conditions such as anxiety, depression, migraine, sleep and cognitive disorders.

There is an observed two-way relationship with common underlying mechanisms and presumed genetic and environmental factors between epilepsy and these disorders<sup>4</sup>. Cognitive dysfunction is one of the most challenging conditions encountered in patients with epilepsy, with a high percentage of self-reported impairments in cognitive functioning among patients with epilepsy. Several factors such as type and frequency of seizures, age at the onset of epilepsy, duration of illness, and antiepileptic drugs (AEDs) can affect the degree of cognitive impairment in patients with epilepsy<sup>5-8</sup>. It is often presumed that AEDs are one of the main causes of cognitive impairment in patients with epilepsy; however, the role of AEDs in cognitive functioning is considered to be dual, and not necessarily

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negative. Evidence supporting the impact of individual AEDs on cognitive functioning is still limited due to the conflicting results from the reported observations<sup>9,10</sup>. This can be explained by the fact that AEDs do not only worsen cognitive performance but also enable some degree of cognitive improvement by reduction of seizure activity. The presumption that polytherapy is more likely to worsen cognitive performance than monotherapy has been questioned. It has some degree of higher risk for cognitive adverse effects; however, it is usually dependent on the combination of AEDs used<sup>11,12</sup>. Event related potentials (ERPs) have been used for studying cognitive brain functions. Sutton *et al.* were the first to report that P300 component of ERPs is related to the subject's reaction to stimulus and found that ERPs are associated with cognitive functions<sup>13</sup>. P300 is a late component of ERPs that is widely used in psychophysiological studies to assess cognitive functions such as memory, attention, concentration, and mental processing. Oddball paradigm is used to record the wave. It uses two different stimuli, i.e. frequent and less-frequent presentation of the target stimuli and frequent presentation of the nontarget stimuli<sup>14</sup>. According to Zhong *et al.*, a number of studies showed significant difference in the P300 latencies and amplitude in patients with epilepsy compared with general population<sup>15</sup>. Patients with epilepsy have longer P300 latencies and lower P300 amplitude<sup>15</sup>.

The aim of this study was to evaluate the effect of AED monotherapy and polytherapy on cognitive functions by assessing P300 in patients with epilepsy and compare them to the results of healthy individuals.

## Patients and Methods

The study was conducted at the Osijek University Hospital Centre, Department of Neurology, and included 164 subjects, of which 82 patients with epilepsy taking AEDs as mono- or polytherapy (49 male and 33 female; mean age 29.5 (range 25-41)) and 82 healthy individuals (49 male and 33 female; mean age 33 (range 23-45)). Patients with epilepsy were divided in two groups according to therapy regimen, i.e. monotherapy group and polytherapy group. Control group consisted of age- and gender-matched healthy subjects without any complaints and not receiving any drugs. Detailed medical history was obtained in each subject.

The inclusion criteria for patients with epilepsy were age 18-65 years and diagnosis of epilepsy based on the International League Against *Epilepsy* classification of epilepsies<sup>16</sup>. The exclusion criteria were age above 65 years, head trauma, stroke, brain tumor, alcohol abuse, ear pathology, and psychiatric disease in medical history. Auditory P300 potentials were recorded and analyzed in all subjects. P300 recordings were performed in a silent room in sitting position using a Medelec Synergy EMG/EP 5-channel device (VIASYS Healthcare Inc., NeuroCare Group, Madison, WI, USA). The international 10-20 system was used for electrode placement with impedance less than 5 K $\Omega$ . Stimuli were delivered *via* headphones binaurally with 65-dB sound pressure level intensity. Electrical signals were filtered with 40-Hz high-pass and 0.1-Hz low-pass filters. A 700-ms time window was used. Recordings were performed using frontal (Fz), parietal (Pz) and vertex (Cz)-located Ag/AgCl electrodes. Referral electrode was right Mastoid (M2). The non-target (regular) tone (1000 Hz) was occurring 80% of the time and the target (irregular) tone (2000 Hz) was occurring 20% of the time during testing. Patients were instructed to discriminate target and non-target stimuli, to count irregular tones, and report their results to a trained technician.

The study was approved by the institutional Ethics Committee. Informed consent was obtained from all subjects participating in this study.

## Statistics

Numerical data were described by basic measures of median and scatter. The normality of distribution of the observed numerical variables was tested by Kolmogorov-Smirnov test. Categorical variables were described by absolute and relative frequencies. Mean values of continuous variables were expressed as median and range for variables that were not normally distributed. Nominal indicators were presented by frequency distribution by groups and share.

Mann-Whitney test was used to investigate differences between two independent groups, and Kruskal Wallis test was used for three or more independent groups. Differences between categorical variables were tested by the  $\chi^2$ -test and Fisher exact test. Correlation between parameters was determined by Spearman correlation coefficient. To assess the significance of the

results obtained, the level of significance was set at  $\alpha=0.05$ .

**Results**

Of the 82 patients with epilepsy, 34 (41.5%) patients were on monotherapy and 48 (58.5%) patients were on polytherapy with two or more AEDs. The duration of P300 latencies in epilepsy group (median 340 ms, interquartile range (IQR) 31.25) was significantly

prolonged compared to control group (median 313 ms, IQR 31.25;  $p<0.001$ ). N200-P300 amplitudes were significantly lower in patients with epilepsy (median 9.50  $\mu\text{v}$ , IQR 7.30) compared to control group (median 13.55  $\mu\text{v}$ , IQR 17.40;  $p=0.001$ ) (Table 1).

*Table 1. P300 latencies and amplitudes in patients with epilepsy and control group*

	Median (IQR)		p*
	Epilepsy patients	Control group	
P300 latency (ms)	340 (31.25)	313 (31.25)	<0.001
N200-P300 amplitude ( $\mu\text{v}$ )	9.50 (7.30)	13.55 (17.40)	0.001

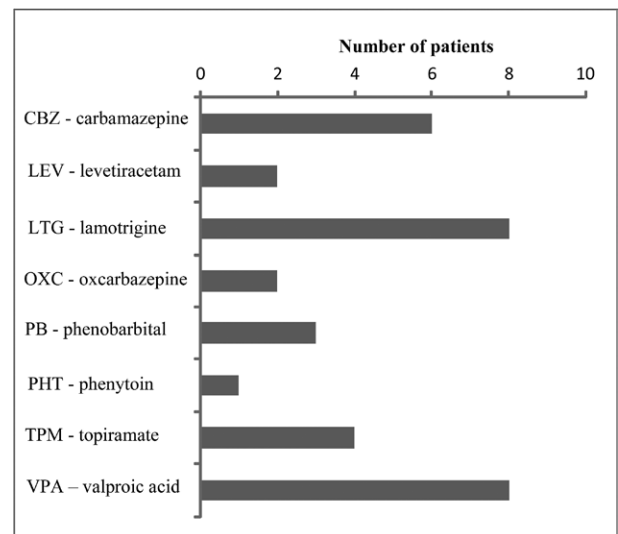
IQR = interquartile range; \*Mann-Whitney test; ms = milliseconds;  $\mu\text{v}$  = microvolts

*Table 2. P300 latencies and N200-P300 amplitudes in patients with antiepileptic drug monotherapy and polytherapy*

	Median (IQR)		p*
	Antiepileptic drugs		
	Monotherapy	Polytherapy	
Latency P300 (ms)	323 (41.25)	348.5 (35.70)	0.004
Amplitude N200-P300 ( $\mu\text{v}$ )	12.1 (8.90)	9.21 (5.80)	0.030

IQR = interquartile range; \*Mann-Whitney test; ms = milliseconds;  $\mu\text{v}$  = microvolts

Comparison of P300 latencies between patients with epilepsy receiving monotherapy and polytherapy indicated that patients receiving AED polytherapy had significantly longer latencies than patients on monotherapy (median 348.5 ms, IQR 35.7 *vs.* 323 ms, IQR 41.25;  $p=0.004$ ). N200-P300 amplitudes in patients receiving AED polytherapy were lower compared to patients receiving AED monotherapy (median 9.21  $\mu\text{v}$ , IQR 5.8 *vs.* 12.1  $\mu\text{v}$ , IQR 8.9), with a statistically significant difference ( $p=0.030$ ) (Table 2). When analyzing patients taking AED monotherapy, we observed the longest P300 latency in patients receiving carbamazepine (CBZ) (median 359.5 ms, IQR



*Fig. 1. Number of patients receiving monotherapy.*

*Table 3. P300 latencies and N200-P300 amplitudes in patients with monotherapy*

	Median (IQR)					p*
	Monotherapy					
	LTG	VPA	CBZ	TPM	PB	
P300 latency (ms)	341.5 (49)	343.5 (67.7)	359.5 (48)	352 (14.8)	357 (53)	0.907
N200-P300 amplitude ( $\mu\text{v}$ )	9.2 (3.6)	9.5 (4.4)	11 (14.4)	10.8 (4.6)	10.2 (11.8)	0.671

IQR = interquartile range; \*Kruskal-Wallis test; ms = milliseconds;  $\mu\text{v}$  = microvolts; LTG = lamotrigine; VPA = valproic acid; CBZ = carbamazepine; TPM = topiramate; PB = phenobarbital

48), and the shortest one in patients receiving lamotrigine (LTG) (median 341.5 ms, IQR 49) (Table 3). Additionally, N200-P300 amplitude was lowest in patients receiving LTG (median 9.2  $\mu$ v, IQR 3.6). Differences in P300 latency and N200-P300 amplitude among patients taking different AEDs were not statistically significant. Figure 1 shows the most common AEDs used as monotherapy.

## Discussion

This study showed that patients with epilepsy had a longer P300 latency and lower P300 amplitude compared to healthy individuals. The result on P300 latency was concordant with the results of meta-analysis published by Zhong *et al.* that indicates a statistically significant difference of P300 latency between patients with epilepsy and healthy individuals<sup>15</sup>.

Antiepileptic drugs have a dual effect on cognitive functions. AEDs can improve patient's cognitive functions by controlling seizures, but some of them can also worsen them, depending on their mechanism of action<sup>9,17</sup>. In order to assess the impact of therapy regimen on cognitive functions, we compared results on P300 latencies and amplitudes between patients receiving AEDs as monotherapy and those receiving AEDs as polytherapy. We found that P300 latencies were longer and P300 amplitudes lower in patients on polytherapy compared to patients on monotherapy. These results are equal to those reported by Triantafyllou *et al.*, who observed 68 patients with epilepsy and found that patients on monotherapy had a shorter P300 latency compared to patients taking two or more antiepileptic drugs<sup>18</sup>. However, some studies report no difference in the aforementioned parameters according to therapy regimen. For example, Ozmeneck *et al.* did not find a statistically significant difference in ERP parameters between patients taking AEDs as monotherapy and polytherapy<sup>19</sup>.

Certain AEDs have been presumed to be involved in the occurrence of cognitive dysfunctions, which are defined as side effects of AED. However, observations from the studies on the effect of AEDs on cognitive functions are contradictory. Phenobarbital (PB) has been reported to be associated with impaired cognitive function in children; according to Chen *et al.*, it improved after discontinuation of PB<sup>8,16</sup>. Similar observations have been reported for valproic acid (VPA). Pana-

gopoulos *et al.* found a significantly prolonged P300 latency in patients taking VPA, while no cognitive impairment was observed in children taking VPA<sup>8,20</sup>. Naganuma *et al.* examined auditory ERP in patients with benign childhood epilepsy with centrotemporal spike and found that P300 latency was significantly prolonged in patients receiving CBZ, but Chen *et al.* failed to detect cognitive impairment in children on CBZ<sup>8,21</sup>. Topiramate (TPM) has the most prominent cognitive adverse events which are dose dependent<sup>22,23</sup>. On the contrary, in patients taking LTG, no clinically significant cognitive effects were observed<sup>24</sup>.

After evaluating all patients on AED monotherapy, we observed that P300 latency was longest in the group of patients taking CBZ, and shortest in patients taking LTG. In contrast, the lowest N200-P300 amplitude was observed in patients taking LTG, and highest in patients taking CBZ.

In our study, there was no statistically significant difference in ERP parameters among AEDs that were used as monotherapy. The possible reasons for such results are a small number of patients on AED monotherapy and the fact that newer AEDs, which were predominant in our group of patients, generally do not have an impact on cognitive functions.

Our study showed that patients with epilepsy had significantly prolonged P300 latencies and significantly decreased N200-P300 amplitudes. Moreover, patients receiving AED polytherapy had significantly longer P300 latencies and significantly lower N200-P300 amplitudes compared to patients on monotherapy. The main limitation of this study was a small sample size; hence, these results should be confirmed in a larger number of patients.

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## Sažetak

UČINAK ANTIEPILEPTIKA NA KOGNITIVNE EVOCIRANE POTENCIJALE P300  
U BOLESNIKA S EPILEPSIJOM*J. Šarić Jurić, S. Jurić, I. Marković, P. Jurić i I. Jurić*

Epilepsija je jedna od najčešćih kroničnih neuroloških bolesti od koje boluje oko 70 milijuna ljudi diljem svijeta. Bolesnici s epilepsijom često imaju poremećaj kognitivnih funkcija uzrokovan početkom bolesti, vrstom epileptičkih napadaja, trajanjem bolesti i antiepileptičkim lijekovima. Kognitivni evocirani potencijali P300 su korisna, neinvazivna, objektivna klinička i istraživačka metoda za ispitivanje kognitivnih funkcija. Cilj ovoga istraživanja bio je ispitati i utvrditi učinak antiepileptičkih lijekova (AEL) u monoterapiji i politerapiji na kognitivne promjene u bolesnika s epilepsijom uz pomoć kognitivnih evociranih potencijala P300 i usporediti ih sa zdravim pojedincima usklađenim prema dobi i spolu. U ispitivanju je sudjelovalo 82 bolesnika s generaliziranom i žarišnom epilepsijom i 82 zdrava pojedinca u dobi od 18-65 godina. Kognitivni evocirani potencijali P300 su snimani koristeći slušnu *oddball* paradigmu. Rezultati ove studije ukazuju na to da bolesnici na politerapiji AEL imaju značajno produženu latenciju vala P300 i značajno nižu amplitudu N200-P300. Prema rezultatima ove studije može se zaključiti kako politerapija AEL u bolesnika s epilepsijom može dovesti do pogoršanja kognitivnog poremećaja.

Ključne riječi: *Antiepileptici; Epilepsija; Kognitivni evocirani potencijali P300; Kognitivni poremećaj*