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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The impact of certain anti-seizure medications on cognitive status, behavior, anxiety, and depression in school-aged children with newly diagnosed epilepsy – a six-month follow-up study

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SUMMARY

Introduction/Objective Previously, we have shown that six months after initiating monotherapy in school-age children with new-onset uncomplicated epilepsy, minimal changes in cognition and significant symptoms of anxiety, depression, and behavioral changes were observed.
In the same group of children, we aimed to show and compare the effects of the most commonly used anti-seizure medications (ASMs) on cognition, psychopathological symptoms, and behavior, to provide guidance in selecting appropriate ASMs.

Methods Children with newly diagnosed epilepsy completed the Revised Wechsler Intelligence Scale for Children in Serbian (REVISK), the Revised Child Anxiety and Depression Scale (RCADS), and the Nisonger Child Behavior Rating Form (NCBRF), immediately after initiating therapy and six months later, at the University Children's Clinic in Belgrade.

Results Scores on the social phobia subscale increased significantly in children on lamotrigine monotherapy compared to other ASMs, as well as on the separation anxiety disorder subscale and total internalizing symptoms in patients on ethosuximide ($p < 0.05$). The scores on the depressive disorder subscale increased significantly in those on ethosuximide, followed by levetiracetam ($p < 0.05$). There is no statistically significant difference in the change of other RCADS scores and REVISK and NCBRF scores between different types of ASMs during the six months ($p < 0.05$).

Conclusion The subtle influence of the tested ASMs was already present during the first six months of treatment. Valproate led to a trend of improved cognition, while ethosuximide and levetiracetam contributed to worsening internalizing symptoms during the first six months.

Keywords: cognition; anxiety; depression; behavior; ASMs

INTRODUCTION

Children with epilepsy experience challenges in behavioral, cognitive, psychological, and emotional functioning. It has been shown that anti-seizure medications (ASMs) may contribute to these issues in different ways [1].

Thus, topiramate (TPM), valproate (VPA), and carbamazepine (CBZ) can significantly adversely affect cognitive status, while the adverse impact of ethosuximide (ESM), levetiracetam (LEV), and lamotrigine (LTG) is minimal, although there are other findings [2, 3].

Some studies have suggested that VPA, LTG, and CBZ may lead to a mood-stabilizing effect in children with anxiety, depression, and bipolar disorder [3, 4, 5]. On the other hand, the same drugs have also been linked to increased anxiety and symptoms of depression in some patients [6]. LEV may also induce anxiety, depression, emotional lability, reversible psychotic symptoms, and behavioral disorders, particularly in predisposed individuals, although there are also other findings [7, 8, 9]. Moreover, after six months of treatment with TPM, children may exhibit varying emotional improvement or deterioration [10].

Previously, we have shown that six months after initiating monotherapy, minimal changes in cognitive functioning and significant symptoms of anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD) were observed [11]. Adverse effects of ASMs significantly contributed only to depressive symptoms (Table 1) [11].

In some cases, the impact of ASMs during the initial months of treatment may be subtle and hard to notice and, in fact, can be a prelude to more serious damage [1]. Therefore, the question remains: What is the subtle influence of antiepileptic drugs on anxiety, depression, behavior, and cognition?

On those grounds, we aimed to evaluate the effects of the most commonly used ASMs on cognition, psychopathology, and behavior in school-aged children with newly diagnosed

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Table 1. Summarized predictors of cognitive status, anxiety, depressive and behavioral disorder symptoms

Predictors		VIQ	PIQ	Anxiety symptoms	Depressive symptoms	ADHD symptoms	Behavior disorder
VIQ	before	▲					
	after						
PIQ	before		▲				
	after						
Anxiety symptoms	before			▲	▲		
	after			▲	▲	▲	
Depressive symptoms	before				▲		
	after		▲	▲	▲		
ADHD symptoms	before					▲	▲
	after				▲		▲
Behavior disorder	before					▲	▲
	after					▲	
Type of ASM					▲		

VIQ – verbal IQ; PIQ – performance IQ; ADHD – attention-deficit/hyperactivity disorder

epilepsy, as well as to determine which antiepileptic drugs contributed most significantly to depressive symptoms. Here, we present the individual effects of these medications during the first six months of treatment to guide the selection of appropriate ASMs.

METHODS

Study design and methodology

The study was designed as a segment of a more extensive prospective study investigating the impact of ASM monotherapy on cognition, behavior, and psychopathological symptoms in school-aged children with newly diagnosed epilepsy. The diagnosis of epilepsy was made based on the definition of the International League Against Epilepsy (ILAE) [12]. It was conducted during two research visits, immediately after initiating therapy and six months later, at the University Children's Clinic in Belgrade in 2020. The selection of ASM was determined independently of the researcher, based on ILAE guidelines [13].

Inclusion criteria were regular psychomotor development, an intelligence quotient (IQ) > 80, normal physiological and neurological status, normal brain MRI, absence of comorbid conditions, and no concurrent therapy. Exclusion criteria included the need to switch the prescribed ASM, the addition of another ASM to therapy (polytherapy), poor compliance, a subsequently discovered structural lesion on the MRI, or an IQ lower than 80 in children whose test results were received after the start of treatment.

Testing and follow-up procedures

After obtaining consent for participation, participants completed a set of questionnaires. During the two research visits, children and/or their parents completed the following questionnaires, and psychological testing was conducted: Revised Wechsler Intelligence Scale for Children in Serbian (REVISK), Revised Child Anxiety and Depression Scale (RCADS), and the Nisonger Child Behavior Rating Form (NCBRF) for typically developing children and adolescents in Serbian.

Questionnaires

Revised Wechsler Intelligence Scale for Children in Serbian (REVISK)

This instrument was used to assess the cognitive status in patients [11, 14]. REVISK is a standardized battery of Wechsler tests tailored to evaluate intelligence and cognitive functioning in children aged 5–15 years, culturally adapted for the Serbian population [14]. REVISK is based on the WISC-R (Wechsler Intelligence Scale for Children) standardization and is psychometrically closest to the WISC-III [15]. It consists of 11 subtests, and scores are calculated relative to age norms and expressed as scaled scores ranging 1–19 [14]. Total scores are reported as verbal IQ (VIQ), performance IQ (PIQ), and total IQ (TIQ). In this study, internal consistency reliability measured by Cronbach's α coefficient was 0.77, 0.86, and 0.88 for VIQ, PIQ, and TIQ scores respectively [11].

Revised Child Anxiety and Depression Scale (RCADS)

RCADS was used to assess anxiety and depressive symptoms [11, 16]. It includes both a self-report and a parent-report version, each containing 47 questions addressing anxiety symptoms (31 questions), depressive symptoms (10 questions), and obsessive-compulsive disorder (OCD; six questions). Higher scores indicate greater presence of global and specific anxious, depression, and OCD symptoms. Psychometric studies have demonstrated reliable and valid measurements in the Serbian version applied in this study [17, 18]. Cronbach's α coefficients for the self-report version were ≥ 0.70 for all scores except for the depression subscale (0.50) [11]. For the parent-report version, the social phobia and OCD subscales had α coefficients of 0.57 and 0.41, respectively, while all other subscale scores had α ≥ 0.78**15** [11].

Nisonger Child Behavior Rating Form TIQ Version (NCBRF)

This rating form was used to evaluate behavior [11]. The questionnaire, completed by parents only, consists of 64 questions rated on a Likert scale from 0 (never) to 3 (always). Scores are calculated by summing item responses. ADHD symptoms are assessed through the hyperactivity and inattention subscales, disruptive behavior disorder symptoms through conduct and compliance subscales, and total externalizing symptoms through the sum of the previous scores. Higher scores indicate greater behavioral difficulties. The questionnaire has demonstrated reliability and validity. In this study, internal consistency reliability measured by Cronbach's α was ≥ 0.76 for all scores except for the hyperactivity subscale (0.56) [11].

Statistical analysis

In this study, the type of ASM was analyzed as an independent variable. The dependent variables included total scores from the REVISK, RCADS, and NCBRF scales. Only adequately completed data from filled questionnaires and tests were included in the analysis.

Descriptive statistical methods used included absolute values, percentages, mean values (M), and measures of dispersion (standard deviation – SD and standard error – SE). Analytical statistical methods included the following tests and analyses: paired t-tests were conducted to assess differences in participants' questionnaire scores at the beginning of treatment (baseline) and after six months of follow-up. For statistically significant changes, the effect size of the score differences was expressed using Cohen's d coefficient, interpreted as small (< 0.5), medium (0.5–0.8), or large (> 0.8) [11]. Analysis of variance (ANOVA) for repeated measures was used to examine the magnitude of score changes in questionnaires over time (baseline and after six months) regarding the type of ASM. All analyses were performed using the PASW Statistics, Version 18.0 (SPSS Inc., Chicago, IL, USA), with a significance threshold of $p < 0.05$.

The study was conducted following Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local and regional regulations, following approval by the Ethics Committee of the University Children's Clinic (UDK) in Belgrade, number 13/208. It was designed as an academic, non-profit, non-interventional clinical study.

RESULTS

The study included 69 school-aged children who were treated at the University Children's Hospital in Belgrade in 2020 who met the inclusion criteria. Nine patients were lost to the six-month follow-up due to poor compliance and necessary polytherapy. The demographic and clinical data of the subjects are presented in Table 2.

Table 2. Clinical data of the subjects

Age (SD), span	All included, n = 68	Followed for 6 months, n = 60
	12.32 (3.34), 7–18	12.45 (3.25), 7–18
Male/female, n (%)	38 (55.9) / 30 (44.1)	34 (56.7) / 26 (43.3)
Antiepileptic, n (%)		
VPA	23 (33.8)	18 (30)
LEV	16 (23.5)	15 (25)
CBZ	14 (20.6)	13 (21.7)
LTG	8 (11.8)	7 (11.7)
ESM	6 (8.8)	6 (10)
TPM	1 (1.5)	1 (1.7)

TPM – topiramate; VPA – valproate; CBZ – carbamazepine; ESM – ethosuximide; LEV – levetiracetam; LTG – lamotrigine

Table 3 shows the mean values (SD) of the REVISK scores for the type of ASM. There is no statistically significant difference in the change in scores between different types of ASM during the six months.

Table 4 shows the mean values (SD) of the subjects' RCADS scores for the type of ASM. Scores on the social phobia subscale increased significantly less than those on the separation anxiety disorder subscale and total internalizing symptoms compared to lamotrigine. The scores on the depressive disorder subscale increased significantly less than those on ethosuximide. There is no statistically significant difference in the change of other scores between different types of ASM during the six months.

Finally, there was no statistically significant difference in the change in NCBRF scores between different types of ASM over the six months (Table 5).

DISCUSSION

The impact of ASMs on cognitive status

Although it was not clinically significant, subtle effects of ASMs on specific cognitive domains were observed.

In our study, VPA demonstrated a positive impact on cognitive status in the first six months. Children receiving VPA therapy showed increased verbal, nonverbal, and overall intelligence quotients. However, the overall effect of VPA did not differ significantly from other ASMs.

VPA, like ESM, is commonly used as a first-line treatment for absence epilepsy. Prior research reported that ESM is more favorable than VPA for cognitive outcomes [19]. However, in our study, during the first six months of treatment, children treated with ESM exhibited a trend of decline in VIQ, PIQ, and overall IQ. Due to the small sample size, this negative impact of ESM on cognition was not statistically significant and does not warrant changes in clinical guidelines for treating absence epilepsy. Nevertheless, our findings suggest that in children with absence epilepsy who present with cognitive deficits at baseline, VPA may be a preferable treatment option.

We have shown that LEV is associated with a trend of decreasing nonverbal IQ, which is novel. However, consistent with earlier observations, LEV was linked to mild cognitive improvement in verbal IQ, attention, and overall cognitive status [20]. While most studies report cognitive abatement following CBZ use [21], our findings indicate mild improvement in VIQ despite a trend of decline in nonverbal IQ domains. It would be useful to see what happens to our subjects later, considering recent studies showing significant cognitive improvement over one year in children treated with LEV and LTG compared to school-aged children treated with CBZ [21, 22]. Of course, this remains a preliminary observation; no significant differences between these drugs were found.

The subtle trend of adverse effects of ESM, LTG, and CBZ on cognitive status during the first six months, though unexpected, highlights the need for further investigation into the cognitive impacts of ASMs. Therefore, we

Table 3. Distribution of REVISK scores with regard to the type of ASM*

IQ	VPA n = 18		LEV n = 15		CBZ n = 13		LTG n = 7		ESM n = 6		Significant differences between ASMs
	M	SD	M	SD	M	SD	M	SD	M	SD	
VIQ before	92.8	11.3	92.1	11.6	95	12.9	98.7	26.4	101.5	20.5	No
VIQ after	93	13.51	86.7	9.2	99.2	13.11	94.1	21.7	96.2	17.2	
PIQ before	93.8	13.2	97	15	108.7	15.11	105.5	17.8	104.3	15.3	No
PIQ after	98.3	17.2	86.7	10.7	105.9	16.3	104.3	16.1	97.51	11	
TIQ before	93.1	10.2	94.1	10.4	101.7	12.5	104	17.5	97.5	11.1	No
TIQ after	95.8	13.9	86.9	9.5	101.9	12.9	100.9	13	97	14	

ASMs – anti-seizure medications; VPA – valproate; CBZ – carbamazepine; ESM – ethosuximide; LEV – levetiracetam; LTG – lamotrigine; VIQ – verbal IQ; PIQ – performance IQ; TIQ – total IQ;
*ANOVA for repeated measurements, Bonferoni corrected, $p < 0.05$

Table 4. Distribution of RCADS scores about the type of ASM*

Parameter	VPA n = 18		LEV n = 15		CBZ n = 13		LTG n = 7		ESM n = 6		Significant differences between ASM
	M	SD	M	SD	M	SD	M	SD	M	SD	
TotAbefore	10.3	9.4	10.3	5.9	10.5	7.2	17.2	11	14.5	9	VPA < ESM
TotA after	16.1	8	26.9	12.9	20.1	13.6	25	12.2	29.8	10.8	
TotD before	2.7	1.9	1.8	2	2.7	1.5	3.9	2.9	2.2	1.5	No
TotD after	5.7	4.5	7.5	4.3	6.9	3.7	5.1	3.1	10.9	7.1	
Sph before	4.2	3.8	4.7	2.7	3.8	2.9	8.1	4.3	6.3	3.8	VPA < LTG
Sph afer	6.9	2.6	10.9	4.8	7.3	4.9	11.6	5.1	12.8	4.4	
OCD before	1.72	1.82	0.91	0.9	2.2	1.8	2.62	2.2	0.3	0.5	No
OCD after	2.2	2.6	1.9	2	2.5	2.6	3.1	2.6	2.5	2.4	
PD before	1.22	0.8	1.3	1.2	1.3	1.4	2.7	2.1	1.3	0.5	No
PD after	2.7	2.4	3.9	3.6	2.3	2.91	3.3	2.8	5.8	5.6	
SAD before	1.6	2.8	1.5	1.6	1.9	1.9	3.1	3.9	3.7	3	No
SAD after	2.5	3.8	2.7	2.4	1.71	2.2	3.4	3.5	7.8	5.6	
GAD before	2.7	1.9	2.4	1.7	1.8	1.7	2.4	2.1	2.7	1.6	No
GAD after	3.1	1.9	4.8	2.7	2.5	1.7	4.4	3.7	6.7	3.6	
TotINbefore	13	10	12.1	7.3	13.2	8.2	21.1	13.9	16.7	9.8	VPA < ESM
TotINafter	921.8	11.9	34.4	16.7	26.9	16.2	30.1	14.8	50.7	16.7	

ASMs – anti-seizure medications; VPA – valproate; CBZ – carbamazepine; ESM – ethosuximide; LEV – levetiracetam; LTG – lamotrigine; TotA – total score for anxiety; TotD – total score for depression; Sph – social phobia; OCD – obsessive-compulsive disorder; PD – panic disorder; SAD – separation anxiety disorder; GAD – generalized anxiety disorder; TotIN – internalizing symptoms total score;
*ANOVA for repeated measurements, Bonferroni corrected, $p < 0.05$

Table 5. Distribution of NCBRF scores about the type of ASM*

Parameter	VPA n = 18		LEV n = 15		CBZ n = 13		LTG n = 7		ESM n = 6		Significant differences between ASM
	M	SD	M	SD	M	SD	M	SD	M	SD	
ADHD before	5.4	4.7	4.5	3.2	7.3	4.8	7.7	3.8	6.2	4.3	No
ADHD after	10.3	7.1	11	6.7	11.7	7.2	11.7	5.3	15.3	7.7	
TE before	11.6	10	8.8	4.3	15.9	13.2	18.4	10.2	3.3	9.8	No
TE after	22.5	17.7	18.6	16.8	24.5	18.2	16.61	13	31.5	14.3	
DBD before	6.1	5.6	4.31	2.6	8.6	9	10.7	6.6	7.2	5.8	No
DBD after	12.1	10.9	17.7	12.5	12.9	12.5	14.9	8.8	16.2	7.1	

ADHD – attention-deficit/hyperactivity disorder; DBD – disruptive behavior disorder; TE – total externalizing score;
*ANOVA for repeated measurements, Bonferroni corrected, $p < 0.05$

underscore the necessity of individualized approaches to ASM selection and emphasize the importance of monitoring cognitive changes in children undergoing antiepileptic treatment.

The impact of ASMs on anxiety, depression, and behavioral problems

Although antiepileptic treatment did not significantly affect the presence of anxiety symptoms after six months [11], some ASMs were more likely to contribute to anxiety than others. Participants treated with ESM had the highest anxiety scores, followed by those on LEV, LTG, CBZ, and finally VPA, which demonstrated the lowest average anxiety scores.

Among all the ASMs evaluated, VPA was the only one associated with the trend of positive effects on symptoms of social phobia and generalized anxiety disorder. It suggests that VPA has the most favorable effect on anxiety symptoms and, if possible, should be the first-line choice in children with seizures and anxiety. Nevertheless, LTG

and VPA demonstrated favorable effects on obsessive-compulsive disorder symptoms after six months, supporting earlier evidence [23].

It has already been said that this research is part of a larger project in which we showed that ASMs, during the first six months, only contribute to the significant occurrence of internalizing symptoms [11]. Based on these findings, LEV stood out for its effect on the occurrence of depressive symptoms, compared to other ASMs. There is a clinically significant negative effect of LEV on internalizing symptoms, including anxiety and depression, which was recently demonstrated and explained in the population of adult patients with epilepsy [24].

In contrast to previous studies [25], our findings suggest that, like other drugs, LEV did not clinically significantly influence behavioral disorders within the first six months of treatment. However, children on LEV exhibited the most pronounced difficulties with conduct, attention, and social competence, alongside increased hypersensitivity, hyperactivity, and ADHD symptoms. Monitoring these trends over time is essential to determine whether LEV's impact on behavioral issues may become clinically significant in the long term.

According to earlier findings of favorable or neutral effects of LTG and CBZ on ADHD symptoms [26, 27], our study showed their less negative, although not clinically significant, impact on behavioral aspects than other drugs, in the following order: ESM > LEV > VPA > CBZ > LTG.

CONCLUSION

Our study is the first to compare the effects of the most commonly used ASMs on specific domains in cognition (verbal/nonverbal), behavior, anxiety, and depression in the first six months, in one act, in children with new-onset uncomplicated epilepsy.

Considering the subtle improvement in PIQ and VIQ, VPA seems like a good option. Given that we have previously shown that the side effects of antiepileptic therapy can significantly contribute to the appearance of internalizing symptoms after six months [11], the present study suggests that the negative impact of LEV and ESM should be considered in children who develop internalizing symptoms after six months. Regardless, this study compared antiepileptic drugs in a gradational way, so certain conclusions can still be drawn. In children who are on ESM and LEV therapy, the epileptologist should be careful in the event of early signs of behavioral disorder symptoms.

However, our research has several limitations. We did not analyze patients regarding epileptic syndromes, seizure type, the impact of epileptogenesis, and epileptiform discharges on the EEG. Also, it would be useful to continue our research so that the trend of the influence of certain antiepileptic drugs would be statistically more significant and could contribute to recommendations for clinical practice.

Conflict of interest: None declared.

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Утицај појединих антиепилептичких лекова на когнитивни статус, понашање, анксиозност и депресију код деце школског узраста са новодијагностикованом епилепсијом – студија шестомесечног праћења

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САЖЕТАК

Увод/Циљ Претходно смо показали да се шест месеци након почетка лечења деце школског узраста са новодијагностикованом некомпликованом епилепсијом јављају минималне промене у когнитивном функционисању, али и значајни симптоми анксиозности, депресије и поремећаја понашања. У поменутој групи деце процењивали смо и упоређивали ефекте најчешће коришћених антиепилептичких лекова (АЕЛ) на когницију, симптоме психопатологије и поремећај понашања шест месеци након почетка лечења, са циљем да допринесемо смерницама за избор одговарајућег АЕЛ.

Методе Деца са новодијагностикованом епилепсијом тестирана су Ревидираном Вешлеровом скалом за интелигенцију на српском језику, Ревидираном скалом за анксиозност и депресију код деце и Нисонгеровим обрасцем за процену понашања деце, одмах по увођењу терапије и након шест месеци, на Универзитетској дечјој клиници у Београду.

Резултати Резултати на супскали социјалне фобије били су статистички значајно виши код деце на монотерапији ламотригином у поређењу са другим АЕЛ, као и на супскали поремећаја сепарације и укупних интернализацијских симптома код деце на етосуксимиду ($p < 0,05$). Резултати на супскали депресивног поремећаја значајно су се повећали код оних на терапији етосуксимидом, а потом леветирацетамом ($p < 0,05$). Нема статистички значајне разлике у променама осталих резултата на Ревидираној скали за анксиозност и депресију код деце, као ни у резултатима Ревидиране Вешлерове скале интелигенције за децу и Нисонгеровог обрасца за процену понашања деце између различитих типова АЕЛ током првих шест месеци ($p < 0,05$).

Закључак Суптилан утицај испитиваних АЕЛ уочен је већ током првих шест месеци лечења. Валпроат је показао тренд побољшања когнитивних функција, док су етосуксимид и леветирацетам у највећој мери допринели погоршању интернализујућих симптома у том периоду.

Кључне речи: когнитивне функције; анксиозност; депресија; понашање; антиепилептички лекови