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Practical aspects of antiseizure medication treatment in pediatric patients – a helpful guide for pharmacists counseling young patients with epilepsy and their parents

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Abstract

Epilepsy is a common brain disorder which frequently affects pediatric patients (from newborns to adolescents). The cornerstone of epilepsy treatment for most patients is the use of antiseizure medicines (ASM). These medications, when used as monotherapy or in combination, can achieve seizure control in up to 70% of patients with epilepsy. However, despite the availability of effective ASMs, adherence to these medicines in pediatric epilepsy tends to be suboptimal, which may adversely affect the long-term prognosis of pediatric patients. In this regard, pharmacist-led interventions, aimed at increasing the health literacy of patients and their family members regarding epilepsy treatment, have been shown to increase adherence to the prescribed ASMs. These interventions focus on educating patients and parents on the nature of epilepsy and practical aspects related to appropriate ASM use. In this article, we aimed to provide a useful source of information for pharmacists (and other healthcare workers) on how to counsel patients and parents on issues related to starting/using ASM treatment (e.g. appropriate dose titration, managing skipped doses), additional measures that may improve treatment outcomes (e.g. monitoring seizure frequency, avoidance of seizure triggers) and safety risks associated with ASMs (and how to control/mitigate these risks).

Key words: pediatric epilepsy, epileptic seizures, antiseizure medication, pharmacist-led interventions

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Introduction

Epilepsy is a chronic brain disorder characterized by an enduring predisposition of an individual to have recurrent and unprovoked (i.e. spontaneous) epileptic seizures. The epileptic seizure is the hallmark of epilepsy; however, it is well recognized that patients with epilepsy frequently have comorbid psychiatric disorders, learning difficulties and encounter numerous social consequences related to the epileptic disorder (e.g. not being able to have a driver's license or to work in certain professions), which jointly contribute to a substantial reduction in quality of life. Furthermore, epilepsy is associated with premature mortality as a consequence of injuries during seizures (e.g. while driving or swimming), *status epilepticus*, SUDEP (sudden unexpected death in epilepsy), suicide and adverse effects of medications used to control epilepsy. For these reasons, achieving seizure control is of paramount importance for persons with epilepsy, as it can improve the long-term prognosis. It is estimated that around 50 million patients globally have active epilepsy, and pediatric patients are one population where the highest incidence rates are usually observed (1–3).

The cornerstones of epilepsy treatment are antiseizure medications (ASM), which can provide optimal control of seizures in around 70% of patients (when used as monotherapy or in different combinations). Non-pharmacological measures, such as the ketogenic diet (or other forms of low carbohydrate diets like the modified Atkins diet), neurostimulation devices (e.g. vagus nerve stimulation devices) or surgery can be considered in cases where ASMs are ineffective in providing seizure control (2).

Even though there are > 20 available ASMs (Table I) and seizure freedom can be obtained in most patients with epilepsy, the adherence to ASM treatment in pediatric epilepsy is suboptimal. Increasing health literacy of patients with epilepsy and their family members has been proposed as a measure that may help in achieving higher rates of adherence. To this extent, pharmacist-led interventions aimed at increasing knowledge about epilepsy and ASM treatment have been shown to increase adherence to prescribed medications. These interventions usually include providing patients and family members educational support aimed at understanding epilepsy disorders, ASM treatment (rationale and benefits of ASM use, importance of adherence, dosing and timing of administration), potential interactions with food and other drugs, and safety of ASM treatment (how to minimize adverse effect and how to act in case of their occurrence) (4–6).

Table I Overview of antiseizure medications (ASM) that can be used in the pediatric population (as monotherapy and/or adjunctive therapy) (7–9)

Tabela I Pregled antiepileptika koji se mogu koristiti u pedijatrijskoj populaciji (kao monoterapija i/ili deo kombinovane terapije) (7–9)

1st generation ASMs	2nd generation ASMs	3rd generation ASMs
• Benzodiazepines (e.g. clonazepam) • Carbamazepine • Ethosuximide • Phenobarbital • Phenytoin • Valproate	• Gabapentin • Lamotrigine • Levetiracetam • Oxcarbazepine • Tiagabine • Topiramate • Zonisamide	• Brivaracetam • Eslicarbazepine acetate • Lacosamide • Perampanel ASMs indicated for specific **developmental and epileptic encephalopathies:** cannabidiol, fenfluramine, rufinamide, stiripentol, vigabatrin (vigabatrin is *also indicated for drug-resistant focal seizures*)

Note: ASMs available in Serbia are given in blue.

The aim of this article is to provide basic information regarding epilepsy and epileptic syndromes observed during childhood and adolescence, as well as practical guidance on starting ASMs and their application, controlling the risk of adverse effects, and additional measures that can be recommended to children with epilepsy and their family members to optimize treatment. At the end of the introduction section, the reader can find a glossary of important terms related to epilepsy and its treatment, as well as Table II, which gives an overview of the more common types of epilepsy and epilepsy syndromes seen during childhood and adolescence (2, 10–13). Furthermore, Figure 1 is included, providing descriptions of the more common types of epileptic seizures, as well as medications that are effective in their prevention.

Figure 1. Infographic with the description of generalized (tonic-clonic, absence and myoclonic) and focal seizures (prepared according to references 14–19)

Slika 1. Infografika sa opisom generalizovanih (tonično-kloničnih, apsansnih i miokloničnih) i fokalnih epileptičnih napada (pripremljeno prema referencama 14–19)

The article is mainly focused on ASMs which are available and widely used in the Republic of Serbia; however, the reader should be aware that in recent years several new third-generation ASMs have become available. Some of these ASMs are indicated only for the treatment of specific developmental and epileptic encephalopathies and will not be further discussed in the text (see Table I).

Glossary of important terms related to epilepsy	
Epileptic seizure	**A transient behavioral change that occurs due to abnormal neuronal hyperactivity and/or hypersynchronous activity in the brain.** The seizure can consist of various motor signs, sensory symptoms, cognitive and language phenomena, affective and/or autonomic symptoms. Epileptic seizures are typically classified as **generalized** (originating from widespread regions on both hemispheres of the brain), **focal** (originating from one or more localized regions in the brain), or of **unknown onset.** See Figure 1 for a description of selected epileptic seizures.
Epilepsy	Based on clinical and epidemiological characteristics, a person can receive an epilepsy diagnosis if: • They have had two or more unprovoked (or reflex) seizures that occurred more than 24 hours apart; • They have had one unprovoked (or reflex) seizure and have a high risk (> 60%) of further seizures in the following 10 years (e.g. due to structural brain lesions); • One or more seizures and other clinical/EEG characteristics that fulfil the criteria for an epileptic syndrome (see below for definition). **Additional note:** reflex seizures are seizures provoked by specific stimuli (e.g. flashing lights) that would not usually provoke recurrent seizures in people without epilepsy.
Epilepsy syndrome	An epilepsy syndrome is defined as a **characteristic cluster of clinical features** (e.g. age of onset, type of seizures, comorbidities) **and EEG features, often with specific etiological findings** (i.e. the cause of seizures). Defining an epilepsy syndrome in an individual patient has both treatment and prognostic implications (i.e some syndromes have high remission rates). However, in the majority of patients with epilepsy it is not possible to define a specific syndrome. See Table II for more information related to some of the more common epilepsy syndromes seen in childhood and adolescence.
Antiseizure medication vs. antiepileptic or anticonvulsant drug	According to the International League Against Epilepsy (ILAE), the term that should be used to describe medicines currently available for epilepsy treatment is **antiseizure medications.** The term antiepileptic drug is considered inadequate, seeing as the currently available medicines are only effective in preventing symptoms (i.e. seizures), and do not have a direct disease-modifying effect. The term anticonvulsant drug is also considered inadequate, as these medicines can be effective in preventing non-convulsive seizures.

Drug-resistant epilepsy	Epilepsy that was not adequately controlled despite the use of two appropriately chosen (and tolerated) ASM treatment regimens (as monotherapy or combination therapy).
Status epilepticus (SE)	A condition of **abnormally prolonged seizures that can result in long-term consequences** (including neuronal injury/death and functional deficits). There are different forms of SE, but the most severe is tonic-clonic SE (defined as a tonic-clonic seizure lasting longer than 5 minutes).
SUDEP (Sudden Unexpected Death in Epilepsy)	**A sudden, unexpected, non-traumatic and non-drowning death of a person with epilepsy** (with or without evidence that a seizure occurred). The exact cause of SUDEP is not known. SUDEP most commonly occurs during the night and the main risk factor is the presence of generalized tonic-clonic seizures (especially when they are frequent). Achieving seizure control with ASMs is the main prevention strategy in reducing SUDEP risk. SUDEP is rare; however it highlights the importance of achieving seizure control in patients with epilepsy.

Table II Characteristics of selected forms of epilepsy and epilepsy syndromes in childhood and adolescence (14–19)

Tabela II Karakteristike odabranih oblika epilepsije i epileptičnih sindroma kod dece i adolescenata (14–19)

Epilepsy or epilepsy syndrome	Usual age of onset	Types of seizures	Prognosis	Usual treatment
Childhood absence epilepsy (CAE)	• **4–10 years** (*more common in girls*)	• **Absence seizures** • **GTCS occur in ~ 20% of patients** • Seizures can be provoked by hyperventilation (also by photostimulation in some patients)	• Normal development (*learning difficulties and ADHD are possible*) • **Long-term seizure-free remission in 50–70% of patients**	• **Ethosuximide** • **Valproate**[a] • Lamotrigine (*less effective than the previous two ASMs*)
Juvenile absence epilepsy (JAE)	• **9–13 years** (*similar prevalence among girls and boys*)	• **Absence seizures** • **GTCS occur in > 90% of patients** • Seizures can be provoked by hyperventilation (also by photostimulation in some patients)	• Normal development (*learning difficulties and ADHD are possible*) • **Lifelong ASM therapy may be required**	• **Valproate**[a] • **Lamotrigine** • *Ethosuximide not to be used as monotherapy in patients with GTCS*

Juvenile myoclonic epilepsy (JME)	• **10–24 years** (*slightly higher prevalence in girls*)	• **Myoclonic seizures upon awakening** (*usually affecting the upper extremities*) • **GTCS occur in > 90% of patients** • Seizures can be provoked by sleep deprivation or photostimulation	• Normal development (*learning difficulties and ADHD are possible*) • **Low remission rate** (*usually requires lifelong ASM treatment*)	• **Levetiracetam and/or lamotrigine** (*usually prescribed to girls with childbearing potential*) • **Valproate**[a] (*usually prescribed to boys and men*) • Lamotrigine can exacerbate myoclonic seizures in some patients!
Epilepsy with GTCS alone (GTCA)	• **10–25 years** (*similar prevalence among girls and boys*)	• **GTCS** (*usually within 2 hours after awakening*) • No other seizure types • Seizures can be provoked with sleep deprivation (also by photostimulation in some patients)	• Normal development (*learning difficulties and ADHD are possible*) • **Lifelong ASM therapy may be required**	• **Valproate**[a] • **Lamotrigine** • **Levetiracetam** • **Adjunctive therapy:** topiramate[a], zonisamide, lacosamide…
Self-limited epilepsy with centrotemporal spikes (SeLECTS, also known as benign Rolandic epilepsy)	• **3–13 years** (*slightly higher prevalence in boys*)	• **Focal with preserved consciousness** (*usually in the form of perioral paresthesia or perioral jerks which may impair speech*) • Progression to GTCS is possible • **Seizures are infrequent** (*usually occur shortly after falling asleep or just before waking up*)	• **Excellent long-term prognosis** (*virtually all patients achieve complete remission of seizures and ASMs can be discontinued if they were used*)	• **Usually no treatment is needed** (*the use of ASMs has no effect on long-term prognosis*) • Many ASMs can be used if treatment is considered to be justified (carbamazepine, oxcarbazepine, gabapentin, valproate, etc.)
Temporal lobe epilepsies (most common localization-related form of epilepsy)	• **10–20 years,** but possible in any age group (*similar prevalence among male and female patients*)	• **Focal with impaired consciousness** • Auras may precede impairment of consciousness (e.g. sensation of déjà vu or jamais vu, fear, etc.) • Impairment of consciousness lasts 30–60s and is accompanied with oral-buccal and bimanual automatisms • Progression to GTCS is possible (but infrequent)	• **Lifelong ASM therapy often required** • **Frequently drug-resistant** • Often requires combination ASM treatment • Surgery in selected patients	• Most ASMs that are effective for focal seizures • **More commonly used:** lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, gabapentin, zonisamide, lacosamide, topiramate[a]… (*as monotherapy or combination therapy*)

[a]**Valproate and topiramate** – the use of valproate or topiramate is discouraged in girls and women with childbearing potential, seeing as they are associated with the highest risk of fetal malformations and adverse neurodevelopmental outcomes in children who were exposed to them *in utero*.

Abbreviations: ADHD = attention deficit hyperactivity disorder; GTCS = generalized tonic-clonic seizure

ASM treatment in children

Why use ASM?

The main goal of ASM treatment is to achieve complete seizure control (i.e. seizure freedom), with minimal adverse effects due to ASMs. Achieving seizure control is important in order to prevent seizure-related injuries (including potentially fatal injuries), *status epilepticus* and SUDEP, which can all lead to premature mortality in patients with epilepsy. Furthermore, children with epilepsy can have a range of other problems attributed to seizures, such as psychiatric or behavioral problems, or learning difficulties (Table II). Achieving seizure control can potentially help in alleviating some of these manifestations of epilepsy; however, certain ASMs can also worsen associated psychiatric or cognitive manifestations (discussed later in the text) (2, 20, 21).

Choice of ASM

The main factor governing the choice of an ASM is the type of seizure or type of epilepsy syndrome present in the patient (Table II and Figure 1). Patients can experience different types of seizures, and the chosen ASM should ideally be effective in preventing all seizure types present in the patient (and also not be associated with exacerbating other forms of seizures). Seeing as several ASMs can be appropriate based on seizure type, other factors that can influence the choice of ASM include:

- **age and sex of the patient** (e.g. valproate or topiramate are avoided in young girls of reproductive age due to the known high teratogenic risk),
- **susceptibility to adverse effects** (e.g. avoidance of ASMs that can reduce weight in children with low body weight),
- **comorbid medical conditions** (e.g. certain comorbidities may favor or discourage the choice of a particular ASM),
- **dosing regimen** (e.g. ASMs and formulations that can be applied once or twice daily are usually favored) (2, 20).

Starting ASM treatment

Treatment is usually started with a single ASM at a low dose, which is gradually up-titrated until seizure control is achieved or until tolerability issues develop. Appropriate dose titration is essential for the success of ASM treatment, seeing as it can reduce the severity of sedative, coordination and cognitive adverse effects. These adverse effects tend to be prominent when starting treatment and gradual titration enables the patient to develop a tolerance. Furthermore, the risk of idiosyncratic adverse reactions (which can be severe and frequently require drug discontinuation) can also be reduced by slowly increasing the ASM dosage (gradual titration enables desensitization of the patient to the ASM). This is of special importance when initiating lamotrigine treatment (one of the most used ASMs), as rapid dose increases are more frequently associated with cutaneous adverse effects, which can lead to drug discontinuation. Table III presents the

usual starting and target doses of selected ASMs, as well as approximate time needed to achieve the target doses (22–24).

Table III Dosing and duration of titration of selected ASMs for oral administration (7–9)

Tabela III Doziranje i dužina titracije odabranih antiepileptika za oralnu primenu (7–9)

ASM	Dosage forms	Initial dose (with respect to age)	Target dose (with respect to age)	Duration of titration
Carbamazepine	**Immediate release**: oral suspension, tablet	**1 month – 11 years:** 5 mg/kg once daily (at night) or 2.5 mg/kg twice daily **12–17 years:** 100–200 mg once or twice daily	**1 month – 11 years:** 5 mg/kg 2–3 times daily (MDD: 20 mg/kg) **12–17 years:** 200–400 mg 2–3 times daily (MDD: 1800 mg)	**Slow titration** (~ 4 weeks needed to reach target maintenance dose)
	Prolonged release: tablet	**5–11 years:** 5 mg/kg daily, in 1–2 divided doses **12–17 years:** 100–400 mg daily, in 1–2 divided doses	**5—11 years:** 10–15 mg/kg daily, in 1–2 divided doses (MDD: 20 mg/kg) **12–17 years:** 400–1200 mg daily, in 1–2 divided doses (MDD: 1800 mg)	
Ethosuximide	**Immediate release**: oral solution, capsules	**1 month – 5 years**: 5 mg/kg, twice daily (max. 125 mg per dose) **6–17 years**: 250 mg, twice daily	**1 month – 5 years**: 10–20 mg/kg, twice daily (max 500 mg per dose) **6–17 years**: 500–750 mg, twice daily (MDD: 2000 mg)	**Slow titration** (~ 4 weeks needed to reach target maintenance dose)
Gabapentin	**Immediate release**: oral solution, tablet, capsule	**Monotherapy:** **12–17 years:** 300 mg once daily **Adjunctive therapy**: **2–5 years:** 10 mg/kg, once daily **6–11 years:** 10 mg/kg, once daily **12–17 years:** 300 mg once daily	**Monotherapy:** **12–17 years:** 900–3600 mg daily, in 3 divided doses **Adjunctive therapy**: **2–5 years:** 30–70 mg/kg daily, in 3 divided doses **6–11 years:** 25–35 mg/kg daily, in 3 divided doses (MDD: 70 mg/kg) **12–17 years:** 900–3600 mg daily, in 3 divided doses	**Rapid titration possible** (maintenance doses may be achieved in ~ 2 weeks)
Lacosamide	**Immediate release**: oral solution, tablets	**4–17 years (≥ 50 kg):** 50 mg, twice daily **4–17 years (< 50 kg):** 2 mg/kg daily	**4–17 years (≥ 50 kg):** 300 mg twice daily (monotherapy) or 200 mg twice daily (adjunctive therapy) **4–17 years (< 50 kg):** 12 mg/kg daily (< 40 kg) or 10 mg/kg daily (40–50 kg)	**Slow titration** (~ 4 weeks needed to reach target maintenance dose) A loading dose can be used in patients > 50 kg for more rapid titration

Lamotrigine[a]	**Immediate release**: dispersible tablets, tablets	**Monotherapy** (focal or generalized tonic-clonic seizures)**:** **12–17 years:** 25 mg, once daily **Monotherapy** (absence seizures)**:** **2–11 years:** 0.3 mg daily, in 1–2 divided doses	**Monotherapy** (focal or generalized tonic-clonic seizures)**:** **12–17 years:** 100–200 mg daily, in 1–2 divided doses (MDD: 500 mg) **Monotherapy** (absence seizures)**:** **2–11 years:** 1–10 mg/kg daily, in 1–2 divided doses (MDD: 15 mg/kg)	**Very slow titration** (~ 8 weeks needed to reach target maintenance dose) Slow titration needed to minimize risk of cutaneous adverse effects **Lower initial doses and slower titration if used concomitantly with valproate!** Higher initial and maintenance doses can be used if the patients is already receiving enzyme-inducing ASMs (e.g. carbamazepine)
Levetiracetam	**Immediate release**: oral solution, granules, tablets	**Monotherapy** (focal seizures)**:** **16–17 years:** 250 mg, once daily **Adjunctive therapy** (focal, myoclonic, and tonic-clonic seizures)**:** **6 months – 17 years (< 50 kg):** 10 mg/kg, once daily **12–17 years (≥ 50 kg):** 250 mg, twice daily	**Monotherapy** (focal seizures)**:** **16–17 years:** up to 1500 mg, twice daily **Adjunctive therapy** (focal, myoclonic, and tonic-clonic seizures)**:** **6 months – 17 years (< 50 kg):** up to 30 mg/kg, twice daily **12–17 years (≥ 50 kg):** up to 1500 mg, twice daily	**Rapid titration possible** (maintenance doses may be achieved in ~ 2 weeks)
Oxcarbazepine	**Immediate release**: oral suspension, tablet	**6–17 years**: 4–5 mg/kg, twice daily (max. 300 mg per dose)	**6–17 years**: 15 mg/kg, twice daily (MDD: 46 mg/kg)	**Slow titration** (~ 4 weeks needed to reach target maintenance dose)
Topiramate	**Immediate release**: oral suspension, tablet, sprinkle capsule	**Monotherapy**: **6–17 years**: 0.5–1 mg/kg, once daily (max 25 mg per dose) **Adjunctive therapy**: **2–17 years**: 1–3 mg/kg, once daily (max 25 mg per dose)	**Monotherapy**: **6–17 years**: 50 mg twice daily (MDD: 500 mg) **Adjunctive therapy**: **2–17 years**: 2.5–4.5 mg/kg, twice daily (MDD: 400 mg)	**Very slow titration** (~ 6 weeks needed to reach target maintenance dose) Slow titration needed to minimize cognitive and other adverse effects
Valproate	**Immediate release**: oral solution, tablet **Prolonged release**: granules, tablet, capsule	**1 month – 11 years:** 10–15 mg/kg daily, in 1–2 divided doses (max. 600 mg per dose) **12–17 years**: 600 mg daily, in 1–2 divided doses	**1 month – 11 years**: 25–30 mg/kg daily, in 2 divided doses **12–17 years**: 1000–2000 mg daily, in 2 divided doses (MDD: 2500 mg)	**Slow titration** (~ 4 weeks needed to reach target maintenance dose)

Zonisamide[b]	**Immediate release**: oral suspension, capsules	**6–17 years (20–54 kg):** 1 mg/kg, once daily **6–17 years (≥ 50 kg):** 1 mg/kg, once daily	**6–17 years (20–54 kg):** 6–8 mg/kg, once daily (MDD: 500 mg) **6–17 years (≥ 50 kg):** 300–500 mg, once daily	**Very slow titration** (~ 4–8 weeks needed to reach target maintenance dose; more rapid titration possible when used in combination with enzyme-inducing ASMs) Zonisamide has a long half-life, and 2 weeks are needed to reach steady state concentrations after each dose adjustment

Abbreviations: ASM = antiseizure medication; MDD = maximal daily dose
[a]**Lamotrigine** – For information related to dose titration when used in combination with valproate or enzyme-inducing ASMs, please see the Summary of product characteristics.
[b]**Zonisamide** – For information related to dose titration when used in combination with enzyme-inducing ASMs, please see the Summary of product characteristics.

Adherence to the prescribed ASM is of paramount importance in the treatment of epilepsy. Skipping ASM doses or rapid discontinuation of ASM treatment can lead to seizure recurrence, injury or even *status epilepticus*. These risks should be emphasized to the parents and other family members. In order to optimize adherence, ASMs that can be administered once or twice daily should be preferred. Additionally, dosing regimens that require the child to administer ASMs during school hours (which can lead to social embarrassment and promote skipping doses) should be avoided if possible. Additional specifics related to ASM administration (timing of administration with regard to meals and advice on how to act when a dose is skipped) are given in Table IV (20, 22).

Table IV Timing of ASM administration with regard to meals and management of skipped doses (25, 26)

Tabela IV Vreme primene antiepileptika u odnosu na obroke i postupanje sa propuštenim dozama (25, 26)

ASMs	Administration with regard to meals	Skipped doses
Carbamazepine	Administer with meals or a large volume of water to minimize gastrointestinal adverse effects Do not chew the tablet (especially extended release tablets)	**ASMs administered once daily** (e.g. lamotrigine, zonisamide, carbamazepine extended release) The missed dose can be given **up to 12 hours after the ASM should have been administered** (if more than 12 hours have passed, the dose should be skipped)
Ethosuximide	Administer with food (or milk) to reduce gastrointestinal adverse effects Do not chew the capsule	
Gabapentin	May be administered with or without food (food may reduce gastrointestinal adverse effects) Capsule content can be sprinkled on soft food in cases of swallowing difficulties (do not chew the capsule content)	
Lacosamide	May be administered with or without food Do not chew the tablets	**ASM administered twice daily** (e.g. levetiracetam, lacosamide, ethosuximide, oxcarbazepine, topiramate) The missed dose can be given **up to 4 hours after the ASM should have been administered** (if more than 4 hours have passed, the dose should be skipped)
Lamotrigine	Administer in a fasted state (food may reduce absorption) Tablets can be crushed and mixed with soft food (do not chew the crushed tablet) Dispersible tablets may be chewed	
Levetiracetam	May be administered with or without food Tablets can be crushed and mixed with soft food (do not chew the crushed tablet) Oral solution can be mixed with a small volume of juice Granules can be mixed with soft food (do not chew the granules)	
Oxcarbazepine	May be administered with or without food Do not chew the tablets	**ASM administered three times per day** (e.g. gabapentin) If the patient forgot to administer a dose of the ASM, **that dose should be skipped,** and the next one administered according to the regular dosing schedule
Topiramate	May be administered with or without food Tablets can be crushed and mixed with soft food (do not chew the crushed tablet)	
Valproate	Administer with food or a large volume of water to minimize gastrointestinal adverse effects Oral solution should not be mixed with carbonated beverages (can cause local irritation of the mouth/throat)	
Zonisamide	May be administered with or without food Capsule content can be mixed with soft food (do not chew the capsule content)	**Never give two doses of the ASM at the same time!**

When using liquid formulations → **measure the right amount of medication with a syringe or medical spoon (do not use a kitchen spoon)**

Additional measures to improve ASM treatment outcomes

Monitoring efficacy

The principal goal of ASM treatment is to achieve seizure freedom, i.e. to eliminate seizure recurrence. To this end, monitoring the number of seizures in a pediatric patient and keeping a seizure diary can help in assessing the effectiveness of the prescribed ASM. In order to properly determine the number of seizures, parents, other family members and people who come into frequent contact with the child with epilepsy should be informed on how to recognize potential epileptic seizures. Convulsive seizures (such as generalized tonic-clonic seizures) are easy to recognize; however, some types of seizures (e.g. absence seizures) can be overlooked if the person observing the patient is not informed on the nature of the seizure (see description of different epileptic seizure types in Figure 1). People observing the seizure should pay attention to:

- **Behavior before the seizure** (e.g. whether the patient reported any unusual sensations before the start of the seizure, what the patient was doing just before the seizure),
- **Behavior during the seizure** (e.g. whether there were changes in awareness, whether the patient was responsive to questions, whether there were movements and changes in muscle tone, which side of the body was affected by the seizure, whether there was loss of urine or bowel control) – sometimes it may be useful to record a seizure while it is happening, as it can help doctors determine the exact type of epileptic seizure,
- **Behavior after the seizure** (e.g. whether the patient remembers what occurred during the seizure, whether they feel tired/sleepy after the seizure, whether they are able to answer questions).

The description of a particular seizure can be noted in the patient's seizure diary, and it could be helpful to the doctor in determining whether the ASM is appropriate for the patient or if changes need to be made to the prescribed ASM treatment (20, 27).

Avoidance of seizure triggers

In patients with epilepsy, certain lifestyle or physiological factors and substances can provoke seizures. Identification of seizure triggers is important for children with epilepsy and their parents, as it can enable them to take steps to avoid them, which can lead to a reduction in the number of seizures. Some of the possible seizure triggers include:

- **Skipped ASM doses** (see Table IV for instructions how to manage missed doses),
- **Irregular sleeping patterns and lack of sleep** (e.g. seizures can be provoked by sleep deprivation in many epilepsy syndromes; see Table II),
- **Exercise and physical activity** (possibly due to hyperventilation; see Table II),
- **Infections and fever,**

- **Stress and strong emotions** (usually negative emotions such as anger, fear, and worry are associated with seizure provocation, but positive emotions (e.g. being overly excited) can also lead to seizures),
- **Flashing lights or bright flickering sunlight** (e.g. while driving) – Some patients may have visually-provoked seizures (also known as photosensitive epilepsy), and they are more commonly seen in adolescents than in adults (photosensitivity is observed in some epilepsy syndromes, see Table II). Typically, flashing lights can provoke seizures, but certain patterns (e.g. stripes) and rapid color changes can also trigger a seizure. For these reasons, videogames and cartoons can lead to seizures in children and adolescents. The easiest way to prevent a visually-provoked seizure is to cover one or both eyes (with a hand) when exposed to flashing lights (simply closing the eyes is usually not sufficient as light may penetrate the eyelids). Furthermore, for children who like to play videogames, reducing the brightness of the screen, reducing screen contrast by playing videogames in a well-lit room and maintaining a reasonable distance from the screen can also help prevent visually-provoked seizures,
- **Alcohol consumption** (especially when more than 2 standard drinks are consumed; alcohol can also increase the severity of ASM adverse effects, such as sedative effects and coordination disturbances),
- **Certain medicines** – Seizure provocation is most commonly seen with some antidepressant drugs (e.g. bupropion), analgesics (e.g. tramadol) and stimulant drugs (including illicit stimulants); however, these are not likely to be used by most children or adolescents. On the other hand, certain medicines that are available without a doctor's prescription have also been associated with seizure provocation. These include first-generation antihistamine drugs (most notable diphenhydramine) and nasal decongestants (usually pseudoephedrine). These medicines are often ingredients of products intended for the symptomatic relief of the common cold and other respiratory infections in the pediatric population (some of the available products list epilepsy or seizure history as a contraindication for use). While these medicines will probably not provoke a seizure in every patient, they highlight the importance of proper consultation with healthcare workers before using medicines in children with epilepsy. The effect of hormonal contraception on ASM efficacy is discussed later in the text (27–31).

Educating parents and other family members on how to act in case of seizures

An important aspect of epilepsy treatment is providing adequate first aid to a child that is experiencing a seizure. In seizures with preserved consciousness, it is usually sufficient to just stay with the patient and provide reassurance until the seizure has passed. However, in cases of seizures with impaired consciousness, additional measures may be needed in order to prevent injury or other potential complications related to the seizure.

Moreover, parents should ensure that the child is adequately supervised during situations/activities that might pose a risk of injury if a seizure occurs (typical examples include swimming or physical activity at heights). The general principles of seizure first aid are presented in Table V.

Table V General principles of seizure first aid (27, 32)
Tabela V Opšti principi prve pomoći kod epileptičnih napada (27, 32)

"Stay" 	**Remain with the person until the resolution of the seizure (i.e. restoration of consciousness)** ➢ Measure the duration of the seizure → most seizures last only a few minutes (longer seizures require prompt medical attention) ➢ Comfort the person in cases where consciousness is not impaired
"Safe" 	**Keep the person safe during the seizure** ➢ Guide away from potential harm (sharp objects, streets, etc.) ➢ Do not crowd around the person experiencing a seizure
"Side" 	**Place the person who has lost consciousness in the recovery position (on the side, with something soft under the head)** ➢ Orient the head towards the floor → keeps the airway clear in case of excess salivation, foaming or blood due to bites ➢ Loosen tight clothes around the neck ➢ Breathing may stop during some seizures, however this is usually temporary
Do Not (in seizures with impaired consciousness) 	**Do not restrain the person** → risk of injury (if a person is walking during the seizure guide them to a safe environment) **Do not put objects in the person's mouth** → risk of injury to the person and the one helping them **Do not give any medicines or liquids orally during the seizure duration** → risk of aspiration
Call for emergency help 	• **Seizures that last longer than 5 minutes** (possibility of *status epilepticus*) • **Repeated seizures** (without complete recovery between the seizures) • **Person injured during seizure or has difficulty breathing during seizure** • **Seizure occurred in water** • **First time seizure**
Rescue medicines Most seizures are self-limiting and usually no medicines are required to end a seizure. In certain cases, when seizures are prolonged (> 2 minutes) or occur in clusters, a patient may be prescribed medicines to abort seizure activity. This is usually a benzodiazepine in an appropriate pharmaceutical form which enables application to a patient with impaired consciousness (rectal diazepam, buccal midazolam, intranasal diazepam or midazolam)	

Therapeutic drug monitoring of ASMs

Therapeutic drug monitoring (TDM) refers to the practice of measuring the level of ASMs in biological fluids (usually plasma or serum concentrations) with the aim of correlating the measured ASM concentration to the observed therapeutic or adverse effects. The practice of TDM can be useful in establishing an effective and safe dosage regimen, making ASM dosage adjustments, and confirming patient adherence in order to optimize clinical outcomes. This is especially true for older first generation ASMs that display non-linear pharmacokinetics (e.g. carbamazepine, valproate, and phenytoin), which can make dosage adjustments more difficult to perform. Furthermore, TDM can be helpful in making dosage adjustments and optimizing ASM treatment in pediatric patients, seeing as the pharmacokinetics of ASMs are usually markedly different in children compared to adult patients (e.g. more rapid ASM elimination and higher weight-adjusted ASM dosage requirements), and can also substantially change as the child ages. Reference laboratory ranges for ASM concentrations in biological fluids have been described for most available ASMs. However, seeing as there is high interindividual variability in ASM treatment response, an individual therapeutic concentration should ideally be defined for every patient (i.e. the concentration of an ASM that has empirically been found to provide optimal seizure control in the individual patient) (20, 33).

Safety of ASMs in children and adolescents

Adverse effects are one of the leading causes of ASM treatment failure, either due to early treatment discontinuation or inability to reach common maintenance doses. In pediatric patients, adverse effects tend to be more common and/or more severe compared to adults. Furthermore, ASM adverse effects are also one of the main causes of reduced quality of life in epilepsy, even when seizure control has been achieved. For these reasons, pediatric patients and/or their parents should be encouraged to report any adverse effect potentially attributed to ASM treatment, so that they can be resolved in a proactive manner (see Table VI for measures that can help increase the safety of ASM treatment). Typically, adverse effects associated with ASMs can be grouped in the following categories: neurological, cognitive and psychiatric adverse effects, idiosyncratic adverse effects, adverse effects related to long-term drug exposure (i.e. seen with prolonged use) and teratogenic effects (20, 23, 34).

Neurological, cognitive and psychiatric adverse effects

All ASMs are known to produce similar neurological adverse effects, such as **sedative effects** (drowsiness, tiredness and lethargy) **and coordination disturbances** (e.g. dizziness, vertigo, ataxia, nystagmus, diplopia, tremor), although their severity varies among individual drugs. Benzodiazepines and barbiturates are most commonly associated with the most intense sedative effects, whereas coordination disturbances are possible with all ASMs (including second and third generation ASMs) (20, 23).

Additionally, ASMs can also have significant effects on **cognitive abilities** and lead to reductions in attention, memory impairment, problems with language skills, difficulty concentrating, impairment of comprehension and problem-solving skills. These adverse effects are of particular interest in children and adolescents, seeing as they have the potential to affect learning and education in critical phases of their development. Cognitive adverse effects are possible with all ASMs (especially when applied in high doses or in combination). As with sedative effects and coordination disturbances, cognitive adverse effects are most prominent with benzodiazepines and barbiturates. Among newer ASMs, topiramate and zonisamide are associated with the most pronounced negative effects on cognitive function, whereas lamotrigine, levetiracetam and oxcarbazepine have a lower potential to significantly alter cognitive functioning. Lamotrigine and levetiracetam can also potentially improve cognitive functioning in patients with epilepsy by effectively controlling seizure activity (20, 35, 36).

Psychiatric adverse effects are also common with ASMs and include behavioral or personality changes (e.g. irritability, hyperactivity, agitation, aggressive behavior and anxiety), as well as mood disorders. It should be noted that uncontrolled epilepsy can also predispose the patient to psychiatric comorbidities, and patients with epilepsy usually have higher rates of anxiety disorders, depression and even psychotic disorders. In this respect, certain ASMs (by controlling seizures) can have a beneficial effect on psychiatric comorbidities present in patients. Among the newer ASMs, levetiracetam can often produce behavioral changes in children (agitation and aggressive behavior) which might necessitate dose reductions or even changes in ASM treatment. Topiramate and zonisamide are also associated with a higher risk of producing psychiatric adverse effects compared to other newer ASMs. Interestingly, several (mostly retrospective) studies have suggested that pyridoxine (vitamin B6) supplementation may be effective in reducing levetiracetam-induced neuropsychiatric adverse effects; however, the quality of evidence is still too low for any formal recommendations (20, 37, 38).

Idiosyncratic adverse effects

The use of ASMs can lead to several different, potentially severe, idiosyncratic adverse effects, which require drug discontinuation. Most idiosyncratic reactions are thought to be immune-mediated hypersensitivity reactions. They are dose-independent and usually occur in the first weeks upon starting treatment. The most notable ones are cutaneous, hematological, hepatic and pancreatic adverse effects (20, 23, 34).

Cutaneous adverse effects are the most common form of idiosyncratic reaction to ASMs and are usually associated with the use of aromatic ASMs (lamotrigine, carbamazepine, oxcarbazepine, zonisamide, phenytoin, phenobarbital). However, they can also occur with other ASMs (at a lower rate compared to aromatic ASMs). They are usually in the form of a maculopapular rash, but may progress to serious skin reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis or drug rash with eosinophilia and systemic symptoms (DRESS; formerly known as anticonvulsant hypersensitivity syndrome). There is a high degree of cross reactivity between different

aromatic ASMs, so if a patient develops a severe cutaneous reaction to one medicine, a different aromatic ASM should in general be avoided. Lamotrigine is particularly well-known for its ability to provoke cutaneous reactions; for this reason, the duration of dose titration is relatively long in order to allow the desensitization of the patient. Furthermore, lamotrigine (and other aromatic ASMs) can lead to phototoxic or photoallergic skin reactions in some patients (20, 23, 34, 39).

Hematological adverse effects (e.g. agranulocytosis, aplastic anemia, and pancytopenia) are possible with several ASMs, most commonly with carbamazepine, but also with valproate, ethosuximide and phenytoin. Significant **drug-induced hepatotoxic effects** are usually associated with the use of valproate (especially in young children, and children who are using several ASMs), but are also possible with other ASMs (e.g. carbamazepine and phenytoin). Furthermore, hepatic damage can also occur within DRESS. Additionally, valproate therapy can lead to drug-induced pancreatitis (especially in younger patients). Routine laboratory monitoring of complete blood counts and/or hepatic enzymes is usually not effective in the timely detection of idiosyncratic adverse effects. For that reason, young patients and their parents should be educated on how to recognize signs and symptoms suggestive of potentially dangerous adverse effects (see Table VI) (20, 34).

Adverse effects in prolonged ASM use

Prolonged use of certain ASMs is associated with the development of specific adverse effects such as changes in body weight, reduced bone mineral density (and increased risk of fractures) and increased risk of kidney stone formation (20, 23).

Increases in body weight are most prominent with valproate, gabapentin and, to a lesser extent, with carbamazepine. An increase in body weight can lead to the development of other cardiometabolic risk factors (such as hypertension, type 2 diabetes and dyslipidemia). On the other hand, topiramate and zonisamide are two ASMs known to reduce body weight. This effect can be beneficial in overweight or obese patients; however, it can also be problematic in children who are underweight, as it may compromise normal growth and development (20, 23).

ASMs can also have a negative effect on bone health and lead to **reduced bone mineral density and increased risk of fractures**. Enzyme-inducing ASMs (carbamazepine, topiramate, phenytoin, phenobarbiton) and valproate are ASMs that are usually linked to decreased bone mineral density, and this adverse effect is attributed to alterations in vitamin D metabolism. No guidelines exist for preventing loss of bone mineral density in patients with epilepsy; measuring vitamin D levels and vitamin D supplementation in deficient patients are reasonable strategies in patients who are in prolonged treatment with these ASMs (20, 40).

Specific adverse effects associated with zonisamide and topiramate

The use of zonisamide and topiramate can lead to oligohydrosis (decreased or impaired sweating) and increase the risk of overheating and heat stroke in children.

Children using these two ASMs should maintain adequate water intake and avoid heavy exercise (especially in hot weather). Additional specific risks seen with the use of zonisamide and topiramate are **metabolic acidosis (decreased serum bicarbonate levels) and nephrolithiasis**. Adequate hydration, apart from preventing overheating, can also be useful in reducing the risk of nephrolithiasis (8, 20, 25).

Teratogenicity of ASMs

A specific risk of ASM treatment seen in adolescent girls and young women of childbearing potential is the teratogenicity of ASMs. Virtually all ASMs can lead to congenital malformations if the patient becomes pregnant; however, the absolute risk differs among individual ASMs. The lowest risk of congenital malformations is associated with the use of lamotrigine, levetiracetam and oxcarbazepine, and these ASMs are usually preferred in girls and young women of childbearing potential (if they can be used based on the type of seizure a patient has). Valproate treatment carries the highest risk of congenital malformations (in around 10% of pregnancies, compared to 1–3% in women not receiving ASM treatment). Furthermore, *in utero* exposure to valproate is linked to several adverse neurodevelopmental outcomes in the offspring. More specifically, children exposed to valproate during pregnancy have a higher risk of developing autism specter disorders and attention deficit hyperactivity disorder, as well as a higher risk of having lower IQ values. Due to these risks, valproate should generally not be used in female patients with childbearing potential. If its use cannot be avoided (i.e. seizure control is only possible with valproate), highly effective contraceptive measures should be in place to prevent an unwanted pregnancy. In recent years, due to the risk of congenital malformations and negative neurodevelopmental outcomes in the offspring, topiramate use has also been discouraged in female patients of childbearing potential, with similar pregnancy prevention strategies recommended as in the case of valproate therapy (41–43).

Table VI Measures to improve the safety of ASM treatment (20, 23, 26)

Tabela VI Mere za unapređenje bezbednosti terapije antiepilepticima (20, 23, 26)

Prevention 	➢ **Choose an ASM suitable to the characteristics of individual patients,** e.g.: • Avoid ASM with prominent psychiatric adverse effects in patients with a history of psychiatric disorders • Avoid ASM associated with weight gain in overweight or obese children • Avoid valproate and topiramate in girls of childbearing potential ➢ **Consider measuring vitamin D levels and/or vitamin D supplementation in patients after long-term treatment with enzyme-inducing ASMs or valproate** ➢ **Use adequate sun protection in patients receiving ASMs with high risk of cutaneous reactions** (e.g. lamotrigine) ➢ **Increase water intake (6–8 glasses per day) in children on topiramate or zonisamide therapy**
"start low and go slow" 	➢ **Risk of neurological, cognitive and psychiatric adverse effects can be reduced by starting ASM treatment with a low dose, and gradual up-titration** ➢ **Risk of idiosyncratic adverse effects (e.g. cutaneous reactions) can be reduced by gradual dose titration**
Educate patients on how to recognize severe adverse effects 	➢ **Patients and parents should be informed that the development of certain signs and symptoms requires prompt medical attention:** - Skin rashes (especially when associated with fever) - Sudden onset of fever, sore throat, chills, myalgia, diarrhea and mouth ulcers → symptoms and signs suggestive of **agranulocytosis** - Frequent vomiting, abdominal pain, jaundice (yellowing of the skin and eyes) and severe fatigue → symptoms and signs suggestive of **hepatic damage**
Consider dosing adjustments or switching ASMs 	➢ Many adverse effects of ASMs are dose-dependent and can be managed by **dosage reductions or by minimizing the fluctuation of blood ASM concentrations** (e.g. by using extended-release formulations or more frequent application of lower doses) ➢ **Idiosyncratic reactions usually require a switch in ASM.** When switching ASMs, consider the potential for cross-reactivity between different aromatic ASMs
Consult healthcare workers before using other medications 	➢ **Patients with epilepsy or their parents should consult healthcare workers before using any additional medications:** - ASMs may alter the efficacy and safety of co-administered medications - Some medicines may provoke seizures in patients with epilepsy (e.g. non-prescription preparations used for the common cold or allergies)

ASM treatment and potential for pharmacokinetic drug-drug interactions

A significant safety aspect of ASM treatment is the relatively high potential of these medicines to interact with numerous other medications in a clinically relevant manner. First generation ASMs (with the exception of ethosuximide and benzodiazepines) have the highest propensity to alter the pharmacokinetics of other medicines (including other ASMs). Carbamazepine, phenytoin and phenobarbital are potent inducers of different CYP isoenzymes (including the CYP3A4 isoenzyme) and UDP-glucuronosyltransferases (UGT). Seeing as these enzymes are involved in the breakdown of most available medicines that undergo metabolic transformation, the list of potentially significant interactions is long. Carbamazepine is also capable of inducing its own metabolic breakdown (so-called autoinduction), which is responsible for its non-linear pharmacokinetics and shortening of its half-life during prolonged administration. These factors jointly contribute to substantial interindividual and intraindividual variability of carbamazepine pharmacokinetics. Valproate, on the other hand, is a potent inhibitor of UGTs and can usually lead to an increase in blood levels of other medicines. Most second generation ASMs have a less pronounced effect on drug metabolism, but certain ASMs of this generation can alter the pharmacokinetics of other medicines *via* enzyme induction (e.g. oxcarbazepine or topiramate). Furthermore, most available ASMs (with the exception of levetiracetam, gabapentin and pregabalin) undergo significant metabolic transformation, making them prone to pharmacokinetic interactions with other drugs classes which act as inducers or inhibitors of enzymes involved in the metabolism of ASMs. In the next section, a brief overview of selected clinically significant interactions is provided (20, 44).

Interactions between different ASMs

Combined use ASMs is a common practice in epilepsy treatment, and it is estimated that around 25% of patients use 2 or more ASMs to control their seizures. The interaction between two ASMs can be pharmacokinetic and/or pharmacodynamic in nature, and it can lead to changes in the effectiveness or safety of epilepsy treatment. Of particular interest are interactions that require changes in the dosing regimen or length of ASM dose titration. In Figure 2, the reader can find information regarding selected pharmacokinetic interactions between commonly used ASMs that may require dosage adjustments (20, 44).

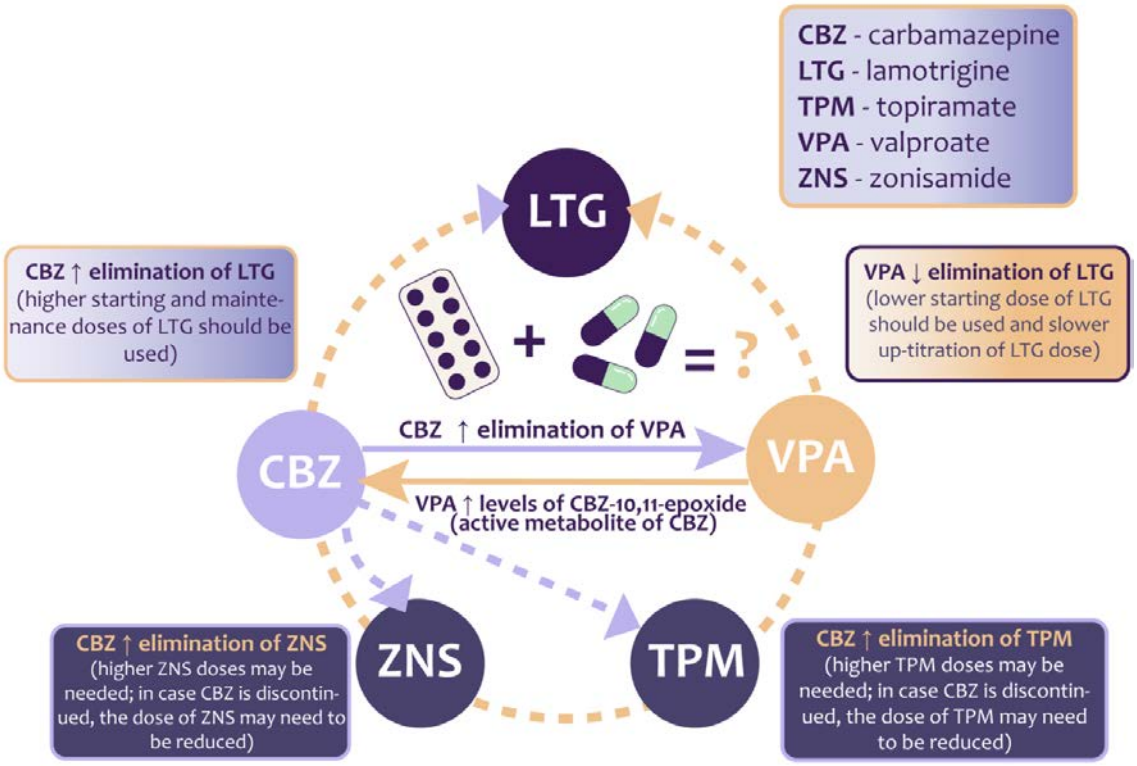

Figure 2. Overview of selected, clinically relevant pharmacokinetic interactions between ASMs (prepared according to references 20 and 44)
Slika 2. Pregled odabranih, klinički značajnih farmakokinetičkih interakcija između antiepileptika (pripremljeno prema referencama 20 i 44)

Interaction between ASMs and hormonal contraception

One of the more important pharmacokinetic interactions in the adolescent population is the ability of some ASMs to diminish the efficacy of hormonal contraception. **Enzyme-inducing ASMs** (carbamazepine, oxcarbazepine, phenytoin and phenobarbital) have the capacity to reduce the levels of ethinylestradiol (the most common estrogen component in hormonal contraception) and different progestins found in combined hormonal contraceptive tablets. Apart from combined contraceptive tablets, enzyme-inducing ASMs can also reduce the efficacy of other forms of hormonal contraception, such as progestin-only tablets, emergency contraception with levonorgestrel, transdermal patches and vaginal rings (progestin intrauterine devices are not affected by enzyme-inducing ASMs). **Topiramate**, when applied in higher doses (> 200 mg/day), can also increase the elimination of ethinylestradiol and reduce the efficacy of hormonal contraception. **Lamotrigine** has no effect on the pharmacokinetics of ethinylestradiol, but it can modestly reduce the levels of levonorgestrel. The clinical relevance of this interaction is not fully established; however, lamotrigine has been shown to increase intermenstrual spotting in users of combined hormonal contraception (which could potentially indicate a compromised contraceptive effect). Other ASMs (valproate,

levetiracetam, zonisamide, gabapentin, lacosamide) do not have a significant effect on hormonal contraception and can be used safely with these preparations. Due to the teratogenic risks associated with valproate and topiramate treatment, most pregnancy prevention programs encourage young female patients to use effective contraceptive measures while receiving valproate or topiramate (e.g. a combined hormonal contraceptive tablet alongside a barrier contraceptive method, or a progestin-only intrauterine device) (45, 46).

It should also be mentioned that certain components of hormonal contraception can alter the pharmacokinetics of ASMs. More specifically, ethinylestradiol-containing hormonal contraception has been shown to reduce the blood levels of lamotrigine and valproate. The effect on valproate is modest and of uncertain clinical relevance. However, the reduction of lamotrigine levels is more substantial and can lead to seizure recurrence. Lamotrigine doses usually need to be increased if the patient wishes to use combined hormonal contraception that contains ethinylestradiol (45, 46).

Conclusion

Epilepsy is a complex brain disorder, and the use of ASMs for its treatment can be challenging, both for patients and their family members. Pharmacist-led interventions aimed at increasing the health literacy of young patients with epilepsy and their parents could help in optimizing adherence to the prescribed ASM treatment and potentially lead to better long-term outcomes. In this regard, the material presented in this article could be a helpful source of information for pharmacists and other healthcare workers while counseling young patients with epilepsy and their family members regarding the nature of epilepsy, and safe/effective use of ASM treatments.

Author contributions

UP: Conceptualization, Writing - Original draft preparation; KN: Writing - Reviewing and Editing, Visualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Praktični aspekti primene antiepileptika kod pedijatrijskih pacijenata – koristan vodič za farmaceute koji savetuju mlade pacijente sa epilepsijom i njihove roditelje

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Kratak sadržaj

Epilepsija je čest neurološki poremećaj koji se može razviti kod pedijatrijskih pacijenata (od novorođenčadi do adolescenata). Osnova lečenja epilepsije za većinu pacijenata je upotreba antiepileptika (AEL). Ovi lekovi, kada se koriste u monoterapiji ili u kombinaciji, mogu dovesti do kontrole napada kod čak 70% pacijenata sa epilepsijom. Međutim, uprkos dostupnosti efikasnih lekova, adherencija prema propisanim AEL u pedijatrijskoj populaciji je često suboptimalna, što može negativno uticati na dugoročnu prognozu pedijatrijskih pacijenata. U tom smislu, pokazalo se da intervencije farmaceuta, usmerene na povećanje zdravstvene pismenosti pacijenata i članova njihovih porodica u vezi sa lečenjem epilepsije, mogu povećati adherenciju prema propisanim AEL. Ove intervencije se fokusiraju na edukaciju pacijenata i roditelja o prirodi epilepsije i praktičnim aspektima vezanim za upotrebu AEL. U ovom radu, cilj nam je bio da pružimo koristan izvor informacija farmaceutima (i drugim zdravstvenim radnicima) o tome kako savetovati pacijente i roditelje o pitanjima vezanim za započinjanje/korišćenje AEL (npr. odgovarajuća titracija doze AEL, kako postupiti u slučaju propuštanja doza AEL), dodatnim merama koje mogu poboljšati ishode lečenja (npr. praćenje učestalosti napada, izbegavanje okidača napada) i bezbednosnim rizicima primene AEL (i kako kontrolisati/ublažiti ove rizike).

Ključne reči: epilepsija kod dece, epileptični napadi, antiepileptici, intervencije farmaceuta