Recommendations of the Polish Society of Epileptology for the treatment of epileptic seizure in adult patients in Poland: an update

Joanna Jędrzejczak[1], Beata Majkowska-Zwolińska[2,3], Danuta Ryglewicz[4], Ewa Nagańska[1], Maria Mazurkiewicz-Bełdzińska[5]

[1] Department of Neurology and Epileptology, Centre of Postgraduate Medical Education, Warsaw, Poland

[2] Epilepsy Diagnostic and Therapeutic Center, Foundation of Epileptology, Warsaw, Poland

[3] Faculty of Medicine, Lazarski University, Warsaw, Poland

[4] Institute of Psychiatry and Neurology, Warsaw, Poland

[5] Department of Developmental Neurology, Chair of Neurology, Medical University of Gdańsk, Poland

Received March 13, 2019
Accepted for publication on-line March 14, 2019
Published on-line March 27, 2019

Correspondence
Beata Majkowska-Zwolińska
Epilepsy Diagnostic and Therapeutic Center, Foundation of Epileptology
02-952 Warsaw, 122 Wiertnicza str.
beata.m.zwolinska@gmail.com
phone: (48 22) 842 24 92

… Constantly expand my medical knowledge and bring to the knowledge of the medical world all that I can invent and improve.

(Excerpt of the oath of Polish medical schools' graduates, derived from the Hippocrates, 5th century BC).

SUMMARY

Introduction. In 2014, a group of Polish epilepsy experts published recommendations for antiepileptic drug (AED) use in adults with epilepsy. Selection of AEDs was based on the registration and reimbursement status in Poland, evidence of efficacy, and the personal views and experiences of the epilepsy practitioners.

Method. In 2018 previous recommendations were reviewed by the ad hoc group consisting of the authors of the original paper and additional epilepsy experts. As a result of joint work and reaching a consensus, an updated version of these recommendations has been prepared.

Discussion and recommendations. This update focuses on the epileptic seizure type treatment recommendations for initial monotherapy and add-on treatment in adult patients. Some new relevant aspects of treatment with AEDs are addressed, including information on the safety of valproic acid (VPA) in women of childbearing potential.

Key words: antiepileptic drugs • treatment recommendations • choice of AED • valproate in women

Original paper

INTRODUCTION

In 2014, a group of Polish epilepsy experts published recommendations of the Polish Society of Epileptology (PSE) for antiepileptic drug (AED) treatment of epileptic seizures in adult patients (Jędrzejczak et al., 2014). The presented therapy outlines and drug selection were based on the registration of AEDs, their reimbursement status in Poland, daily practice and personal views and experiences of epilepsy practitioners, as well as on the guidelines for the treatment of epilepsy published by the International League Against Epilepsy (Glauser et al., 2006), American Academy of Neurology (French et al., 2004a; 2004b), Scottish Intercollegiate Network Guidelines (SIGN, 2003) and the British Institute for Clinical Excellence (NICE, 2004). In 2018, these recommendations were reviewed by the appointed, extended group of Polish experts from the Board of the PSE, the Foundation of Epileptology and the National Consultant in Neurology. As a result of joint work and reaching a consensus, an updated version of these recommendations has been prepared. This update primarily concerns information on the safety of valproic acid (VPA) in women of childbearing potential and modified recommendations for the treatment of monotherapy in patients with newly diagnosed epilepsy and drug subsequent selection in add-on therapy in adult patients. Update of these recommendations was aimed to meet the expectations of Polish neurologists as well as for decision makers in the national healthcare system. The present recommendations, as were the previous ones, are only general indications, not a set of mandatory rigid rules to follow.

METHOD

For the purpose of developing the recommendations, the following definitions have been used: **monotherapy** refers to the **first-line AEDs**, used usually as first in the therapy. If the chosen drug does not give the expected beneficial effect (lack of efficacy and/or side effects), another drug out of first line category can be used (an **alternative monotherapy**).

Depending on the clinical situation, alternative monotherapies with first-line drugs or add-on therapy may be introduced.

Add-on therapy – a therapeutic option in which another drug from the first or second and third line drugs is added to the first-line drug.

The **third-line** drug can be used when the current therapy with the use of first- and second-line drug is ineffective. Before choosing a third-line medication, it's recommended to consult with a center specializing in epilepsy to verify diagnosis, consider a different combination of AEDs, or consider other non-pharmacological treatments, including neurosurgical treatment. Allocation of the AED to first, second and third line was based on a review of the relevant latest literature on different treatment strategies, level of evidence for AEDs efficacy, international guidelines (Kanner et al., 2018a; 2018b), drug status in Poland (registration, availability and reimbursement) and clinical and daily use experience. Each member of the appointed group of experts expressed his/her comments, and after reaching a consensus, recommendations were made.

DISCUSSION AND RECOMMENDATIONS

The aim of epilepsy treatment is to enable the patients with epilepsy to achieve satisfactory adaptation to the demands of life and to lead lifestyles consistent with their capabilities. In particular, it is about complete seizure control or substantial decrease of its number with the least possible side effects of the treatment. The essential improvement in the standard and quality of life is in line with the patient's perceived decrease in the number of seizures (Harden et al., 2007). On the other hand, however, it is known that people with epilepsy in their everyday life are exposed to the vast variety of objective and subjective burdens resulting from their illness (de Boer et al., 2008, Mula and Cock, 2015). Clinicians involved in epilepsy treatment should focus equally on seizure control, as well as on improving the psychosocial functioning of patients with epilepsy. The need of the sense of independence and self-reliance of people with epilepsy in overcoming various psychosocial barriers and superstitions is increasingly being raised.

The decision to choose an AED is the responsibility of the neurologist. However, the general rules of management and treatment should be known to the general practitioners, as well as to other specialists involved in the therapeutic process of epilepsy patients at different stages of their lives. This is particularly important as the comorbidity of other somatic and mental diseases in patients with epilepsy is more frequent than in the general population (Tellez-Zenteno et al., 2005; 2007; Majkowska-Zwolińska et al., 2008). This results in comedication and potential interactions between different drugs (Patsalos et al., 2002, Majkowska-Zwolińska et al., 2011).

The choice of an AED primarily depends on the efficacy of the compound for controlling the patient's seizure type or in a specific epilepsy syndrome. The decision should be made on an individual bases and analysis of the profit-risk ratio of each currently available treatment option. The key element of therapy is the time of its start, the choice of a particular first-line drug and the best strategy for patients who did not respond satisfactorily to the initial therapy. The other patient-specific factors, such as sex, age, comorbidities (including hepatic and renal impairment), and other medications must be taken into account.

With currently more than 20 AEDs available for the treatment of epilepsy in adults, the choice of drug seems to be very vast, but at times it also makes selection of the most suitable drug a complicated task, even for specialists in the field of epileptology.

When to start treatment?

The answer to this question seems simple – when epilepsy is diagnosed. The conceptual definition presented in 2005 by the Working Group of the International League Against Epilepsy (ILAE), defines epilepsy as *a brain disorder characterized by an enduring predisposition to generate epileptic seizures and the resulting neurobiological, psychological and social consequences* (Fisher et al., 2005). The conceptual definition of epilepsy implies that for its diagnosis it is enough to have at least one unprovoked seizure when there is a high risk for the next. This real risk is the subject of discussions and debates.

It is known that after a single unprovoked epileptic seizure, the risk of a second seizure is 40–52% (Berg and Shinnar, 1991). After two unprovoked, non-febrile seizures, the risk of another seizure in the 4-year period is 73%, and with 95% confidence interval – 59–87%. Thus, the approximate risk of subsequent seizures after the first two was set at 60–90% (Hauser et al., 1998). On this basis, a consensus was reached for the diagnosis of epilepsy and, consequently, the initiation of antiepileptic treatment after the second epileptic seizure. From a practical point of view, the most important thing is to understand that the risk of another seizure after the first event varies significantly depending on the characteristics of the patient. In people with risk factors for seizures, such as:

- an underlying condition (stroke, brain injury etc.);
- an abnormal neurological examination;
- the presence of epileptiform discharges on EEG;
- abnormalities on neuroimaging studies suggesting epileptogenic nature;

the likelihood of seizure recurrence after the first one may be similar and comparable with the risk of further seizures after two unprovoked seizures (Hesdorffer et al., 2009). In this case, starting AED treatment seems to be justified, especially if another seizure could affect the patient's professional functioning. This was an argument taken into consideration by the ILAE in developing a new operational (practical) clinical definition of epilepsy in line with the way neurologists treating epilepsy think. The Working Group of the ILAE has extended the definition of epilepsy (Fisher et al., 2014; 2017a; 2017b). Epilepsy should be considered as a brain disease as defined by one of the following conditions:

- at least two unprovoked (or reflex) seizures occurring more than 24 hours apart;
- one unprovoked (or reflex) seizure, and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over next 10 years;
- diagnosis of an epilepsy syndrome.

The new practical definition may improve the effects of the treatment by raising clinicians' awareness of thoughtful management after a single unprovoked seizure. However, since AED therapy, especially in adults, is usually planned for many years or even for life, the decision to start treatment can have far-reaching consequences and must be based on a very thorough analysis of the advantages and risk of AEDs.

New classification of epileptic seizures In the previous and the present recommendations for the selection of the first, second and third-line treatments, the seizures terminology was based on Classification of Epileptic Seizures from 1981 (Commission on Classification and Terminology of the ILAE, 1981). However, since the following recommendations relate to the choice of treatment for specific types of seizures, a new classification of seizures published in 2017 was also considered and the differences in the nomenclature were addressed (Fisher et al., 2017a; 2017b). The major changes in the new classification compared to the previous one is presented below and in Table 1.

- Renaming partial seizures for seizures with a focal onset.

Table 1. The new International League Against Epilepsy 2017 operational classification of seizure types (basic version) (Fisher et al., 2017a)

FOCAL ONSET		GENERALIZED ONSET	UNKNOWN ONSET
Aware	Impaired awareness	Impaired awareness	
• Motor onset		• Motor Tonic-clonic other motor	• Motor Tonic-clonic other motor
• Non-motor onset		• Non-motor	• Non-motor
Focal to bilateral tonic-clonic			Unclassified

- Types of seizures can be classified into either focal, generalized or with an unknown onset.
- Awareness is used as a classifier of seizures with focal onset (with/without impaired awareness).
- Terms such as simple and complex partial and secondary generalized seizures have been removed.
- The new category of focal seizures includes: automatisms, autonomic seizures, behavioral arrest, cognitive, emotional, hyperkinetic, sensory and focal to bilateral tonic-clonic.
- Atonic, clonic, myoclonic, tonic and epileptic spasms may be focal or generalized.
- Generalized-onset seizures can also be nonmotor (absence): typical absence, atypical absence, myoclonic absence, or absence with eyelid myoclonia.

General principles of pharmacological treatment of epilepsy

- The start of treatment must be preceded by a confirmed diagnosis of epilepsy.
- The diagnosis and choice of the AED is the responsibility of the neurologist.
- Treatment is indicated after two epileptic seizures and in special cases it is to consider after the first unprovoked seizure in patients with a high risk of seizure recurrence and when the expected seizures may have serious consequences (e.g. in older adults), especially with the presence of:
  – a neurological deficit;
  – an epileptic discharges on EEG;
  – a structural lesion in neuroimaging, considered to be epileptogenic.
- The explanation to the patient of the possible consequences of seizures and various options for the further management is crucial. The patient should be properly informed and the final decision about starting treatment should be shared.
- Pharmacological treatment of epilepsy should be individually tailored depending on the type of seizure and/or seizure syndrome, co-morbidities and use of co-medications. Other relevant factors include age of the patient (special care groups – children, women of childbearing age, people over 65 yr.) and social factors (education, work, driving license, etc.).
- In women of childbearing age, the possible teratogenic effect of AEDs and their potential negative effects on the fetus is particularly important. In any case, the decision of treatment, its effectiveness, the dose and type of AEDs should be carefully considered.
- It is recommended to start therapy with one drug (monotherapy).
- The diagnosis of epilepsy should be verified if appropriate treatment with first-line drugs does not provide seizure control.
- If seizures are not controlled or if there are side effects when using the first drug, a second drug should be added (another AED from first line drug group) and once the drug is titrated to optimal dose, the first drug should be slowly withdrawn (alternative monotherapy).
- Ad-on therapy is recommended when AED monotherapy does not result in seizure cessation.
- If ad-on therapy is ineffective or poorly tolerated, other second-line or third-line therapy should be considered. Especially in the latter situation, a consultation at a specialist center should be considered.
- There is always a rule of balance between effectiveness (measured by the reduction in the number of seizures) and the tolerance of side effects.

Update of international treatment guidelines in focal epilepsy in adults

The rationale of recommendation of AEDs use was strongly based upon results of recent guidelines in particular prepared by the Sub-Commission of the American Academy of Neurology (AAN) and the American Epilepsy Society (AES) (Kanner et al., 2018a, 2018b). Based on the clinical trial methodology, AAN experts identified three categories of recommendation strength (levels A, B and C) for monotherapy in new-onset epi-

Table 2. Recommendation for the choice of AEDs in monotherapy and add-on treatment in adults with epilepsy according to seizure type

Type of seizure	Monotherapy/Alternative monotherapy I – Line Drugs	Add-on therapy II – Line Drugs	Add-on therapy III – Line Drugs
Focal (Focal onset)	CBZ, GBP, LEV, LTG, OXC, VPA *	CBZ, GBP, LCM, LEV, LTG, PGB, OXC, TPM, VPA *	BRI, ESL, PB, PHT, PER, RFN, TGB, VGB, ZNS
Primary generalized tonic-clonic (Generalized onset motor tonic-clonic)	LEV, LTG, VPA**, To consider: CBZ, OXC	CLB, LEV, LTG, TPM, VPA **, ZNS	
Myoclonic (Generalized onset motor myoclonic) ***	VPA ** To consider: LEV, LTG	LEV, LTG, TPM, VPA **	CLB, CLN, ZNS, piracetam (In Dravet Syndrome to consider: CBD and STR)
Generalized atonic/tonic (Generalized onset motor atonic/tonic) ***	VPA **	LTG To consider: TPM	RFN (In Lennox-Gastaut Syndrome to consider: CBD)
Absence (Generalized onset non-motor) ***	ESM, VPA** To consider: LTG	ESM, LTG, TPM, VPA **	CLB, CLN, LEV, ZNS

* Contraindicated in women of childbearing potential.

** PA treatment must not be used in girls and women, unless alternative treatments are not adequate.

*** CBZ, OXC, GBP, PHT, PGB, VGB, TGB should not be used.

Seizure type according to new classification in parenthesis (Fisher et al., 2017b).

Not all compounds are reimbursed – updates are available on the website of the Ministry of Health and National Health Service.

AEDs in individual columns are shown in alphabetical order: BRI – brivaracetam, CBD – cannabidiol, CLB – clobazam, CLN – clonazepam, CBZ – carbamazepine, ESM – ethosuximide, ESL – eslicarbazepine, GBP – gabapentin, LCM – lacosamide, LTG – lamotrigine, LEV – levetiracetam, OXC – oxcarbazepine, PB – phenobarbital, PER – perampanel, PGB – pregabalin, PHT – phenytoin, RFN – rufinamide, TGB – tiagabine, TPM – topiramate, STR – stiripentol, VGB – vigabatrin, VPA – valproate, ZNS – zonisamide

lepsy and add-on therapy in refractory epilepsy. The latest data regarding efficiency and safety includes 8 second generation AEDs and 6 newer AEDs, so called third generation (eslicarbazepine (ESL), esogabine (EZG – its manufacture has been discontinued), lacosamide (LCM), perampanel (PER), pregabalin (PGB) and rufinamide (RFN) in newly diagnosed epilepsy with a focal onset (Kanner et al., 2018a). Not all of the AEDs are approved and available in Poland. The main conclusions of the report are: lamotrigine (LTG), levetiracetam (LEV) and zonisamide (ZNS) may be considered in the treatment of newly diagnosed focal epilepsy in adults, and LTG and gabapentin (GBP) especially considered in patients ≥ 60 years. Analyzed studies regarding the treatment of newly diagnosed focal epilepsy were limited to comparisons between AEDs of the first and second generation (and vigabatrin – VGB). Felbamate (FBM) and VGB are not recommended for newly diagnosed epilepsy because of serious side effects, especially since there are other drugs that are both safe and effective (Kanner et al., 2018a). The second part of the summary of update on the efficacy and tolerance of new AEDs in the treatment of refractory epilepsy indicates that immediate release PGB and PER are effective in drug-resistant focal epilepsy in adults (level A) as well as VGB (not the first-line drug due to risk of retinopathy) (level A); RFN is effective in the treatment of Lennox-Gastaut syndrome (LGS) in add-on therapy (level A). The following drugs should be considered in drug resistant epilepsy in adults: LCM, ESL and topiramate (TPM) extended release (level B). Clobazam and extended-release oxcarbazepine (OXC) may be considered in drug resistant epilepsy in adults (level C) (Kanner et al., 2018b). It should be mentioned that the NICE guidelines, which include diagnostic and therapeutic procedures in epilepsy and seizures in children, adolescents and adults in primary and specialist medical care, were also updated in April 2018. The most important new statements concern restrictions regarding the use of VPA (NICE, 2018).

Detailed PSE recommendations for selecting AEDs depending on seizure type

Detailed recommendations for selection of the AEDs in focal seizures and generalized seizures in adult patients with newly diagnosed epilepsy and drug-resistant epilepsy are presented in Table 2. Most of the recommendations have not changed since the previous publication in 2014, as no many new treatment options have become available. The results of studies comparing

older and newer drugs indicate similar efficacy of both groups of drugs in newly diagnosed epilepsy. However, new-generation drugs have a more favourable pharmacokinetic profile (Chen et al., 2018).

The studies published in recent years (Villanueva et al., 2013; 2015; Zadeh et al., 2015) and the positive clinical experience of LCM as add-on therapy indicate that this drug is effective and safe in such therapy. It seems to be much more effective when given as early add-on therapy, i.e. in patients who received one or two previous AEDs. This became the basis to allocate LCM as a drug for use in add-on therapy as second-line drug and not a third-line, like in previous recommendations. The presented position of the PSE expert group does not currently change the LCM reimbursement rules, but it may have an impact on this situation, especially since generic formulations have been available since November 2018.

As in previous recommendations some AEDs have been left among third-line drugs used in add-on therapy. The reason for allocation of those AEDs is either lack of/or little experience of Polish neurologists (despite demonstrated efficacy and safety) or high risk of side effects that require special supervision and therefore are rarely prescribed (Table 2). One of these drugs, retigabine (RTG), was withdrawn from the pharmaceutical market in 2017 due to the occurrence of side effects.

Some epileptic syndromes with childhood onset continue also in adult patients. Considering that their clinical picture may include several types of seizures, these syndromes are included in the table, which contains recommendations for treatment of particular types of seizures. Recent studies indicate the potential efficacy of new drugs such as RFN, stiripentol (STR) and cannabidiol (CBD) in the treatment of selected epilepsy syndromes (Devinsky et al., 2017; Thiele et al., 2018).

The use of VPA and its derivatives in women of childbearing age

When using VPA in girls and women of childbearing age, especially in high doses or in polytherapy, the potential risk of malformations and neurodevelopmental disorders in a child should always be discussed. VPA taken during pregnancy can cause developmental defects in 11% of children and developmental disorders in 30–40% of children after birth (Meador et al., 2009, Weston et al., 2016; Bromley et al., 2010).

In 2014, the European Medicines Agency (EMA) issued information on extended safety warnings about medicines containing VPA due to the risk of serious developmental disorders and/or congenital malformations. Subsequently, a group of safety experts from the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA carried out an assessment of the measures taken so far to minimize the risk of birth defects and developmental disorders and expressed its position on March 23, 2018 (European Medicines Agency, 2018). It states that despite previous recommendations to better educate patients about the risks associated with these medicines, women still did not receive the right information at the right time. Therefore, the new measures strengthen earlier restrictions related to the use of valproic acid and its derivatives and to inform women about the risks. New activities include the ban on the use of this group of drugs in the treatment of migraine and bipolar disorder during pregnancy, as well as in the treatment of epilepsy, if another effective form of treatment is available. VPA treatment must not be used in girls and women, including girls under adolescence, unless alternative treatments are not adequate and if the conditions of the pregnancy prevention program are not met. This program includes: assessment of patients for the possibility of pregnancy; pregnancy tests; advising patients on the risk of VPA treatment; explaining the need for effective contraception during treatment; regular (at least once a year) treatment consultation by a specialist and filling out the risk confirmation form. During pregnancy, VPA is contraindicated and alternative therapy should be decided upon appropriate specialist consultations.

Pregnancy Prevention Program

- VPA should not be prescribed to girls and women of childbearing age unless no other appropriate treatment is available.
- Education of the family and/or caretakers.
- When a girl experiences menstruation, it is advisable to contact a specialist and provide appropriate information on the risks.
- We should aim to convert VPA into alternative treatment in girls before sexual maturity.

Pregnancy test

- Before beginning treatment with VPA, pregnancy should be excluded.
- VPA treatment must not be initiated in women of childbearing potential without a negative pregnancy test result (plasma pregnancy test).

Contraception

- Women of childbearing age who have been prescribed VPA must use effective contraception throughout the VPA treatment (e.g. intrauterine device) or two complementary methods (including barrier methods).

Annual treatment checks performed by a specialist

- Once a year, the specialist should assess whether VPA is the most appropriate treatment (form of annual confirmation that the patient has become aware of the risk).

Planning pregnancy

- If a woman plans to become pregnant, a specialist experienced in the treatment of epilepsy needs to reassess the treatment of VPA and consider alternative treatments before becoming pregnant.

In pregnancy

- VPA in the treatment of epilepsy is contraindicated in pregnancy unless there is no alternative treatment;
- The woman should be referred to a specialist to reevaluate the need for VPA treatment and consider another treatment. If the patient needs to receive VPA during pregnancy, the lowest effective dose should be used. Prenatal monitoring should be implemented in all patients receiving VPA during pregnancy.

The full text of the new restrictions on the use of VPA in women of childbearing age and the introduction of a contraceptive program is available on the website of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products.

CONFLICT OF INTEREST

None declared.

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