

National Consensus on Diagnosis and Treatment of Epilepsy

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On the initiative of the Bulgarian Society of Neurology

Today, December 12, 2023, the undersigned specialists reached a consensus on the diagnosis and treatment of epilepsy.

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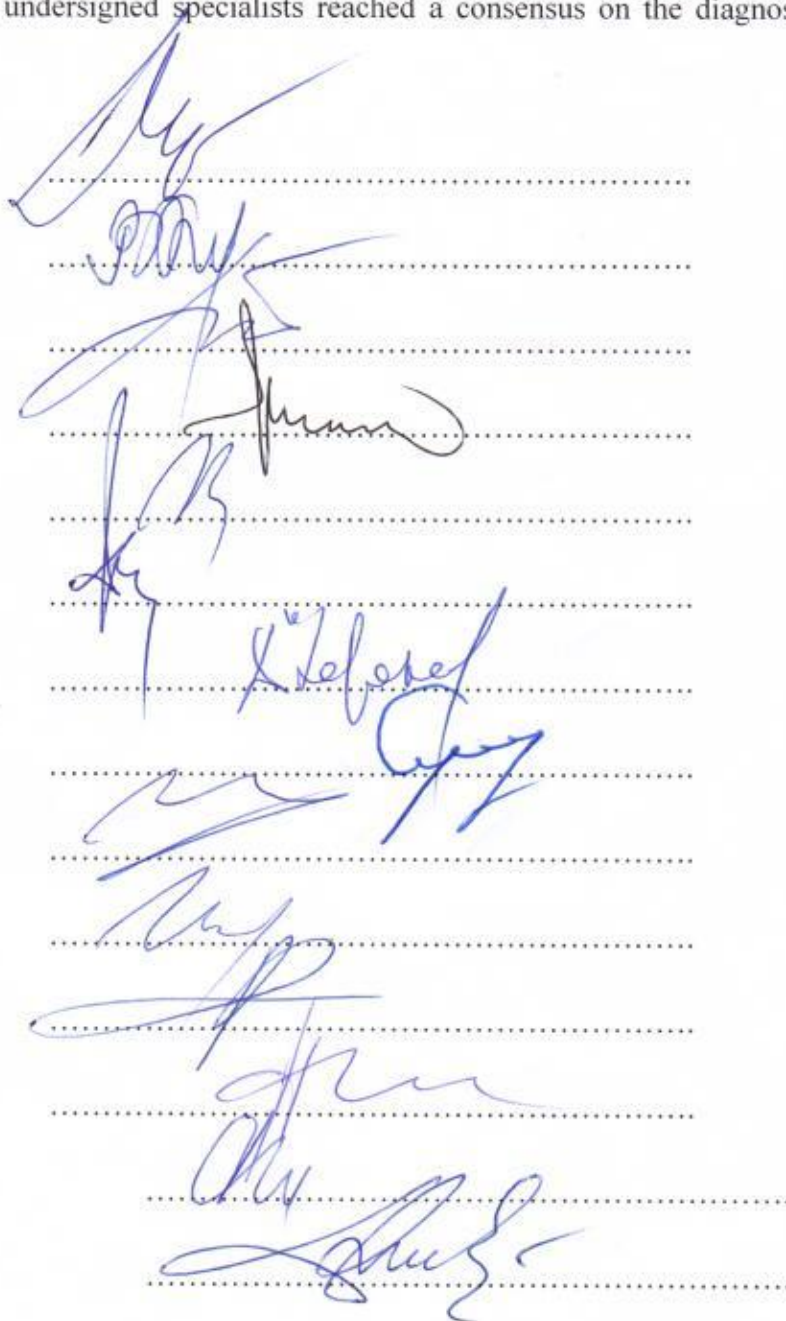


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Glossary of Abbreviations

- ASD – Anti-Seizure drugs
- GTCS – Generalized tonic-clonic seizures
- SGTCS - Secondary generalized tonic-clonic seizures or focal seizures with evolution to bilateral tonic-clonic
- FBTCS - Focal seizures with evolution to bilateral tonic-clonic seizures
- FS – Febrile seizures
- ACTH – Adrenocorticotrophic hormone
- ADNFLE – Autosomal dominant nocturnal frontal lobe epilepsy
- ADPEAF – Autosomal dominant partial epilepsy with auditory features
- BECTS – Benign epilepsy with centrotemporal spikes, Rolandic epilepsy
- BFNS – Benign familial neonatal seizures
- BRV - brivaracetam
- CBD - Cannabidiol
- Cenobamate
- CBZ – Carbamazepine
- Clobazam
- CLZ – Clonazepam
- CSWS – Continuous spikes and waves during sleep
- DNET – Dysembryoplastic neuroepithelial tumor
- ESES – Electrical status epilepticus during sleep
- ESM – Ethosuximide
- ESL – Eslicarbazepine
- FFL - Fenfluramine
- GEFS+ - Generalized (genetic) epilepsy with febrile seizures +
- GBP – Gabapentin
- HS – Hippocampal sclerosis
- FS – Febrile seizures
- CPS – Complex partial seizures
- ILAE – International League Against Epilepsy
- LEV – Levetiracetam
- LTG – Lamotrigine
- LCM- Lacosamide
- OxCBZ – Oxcarbazepine
- PB – Phenobarbital

- PGB – Pregabalin
- PHT – Phenytoin
- SUDEP – sudden unexpected death in epilepsy
- TGB – Tiagabine
- TLE – Temporal lobe epilepsy
- TPM – Topiramate
- SMEI – Severe myoclonic epilepsy in infancy, Dravet syndrome
- VGB – Vigabatrin
- VPA – Valproate
- ZNS – Zonisamide

I. Definition and Epidemiology

1. Definition. The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) define epilepsy as “disorder of the brain characterized by enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition”.

According to the expanded definition of epilepsy of 2014 recommended by ILAE, epilepsy is a disease of the brain defined by any of the following conditions:

1. At least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures (a seizure occurring 30 days after brain stroke in case of established brain structural abnormalities and epileptiform EEG)
3. Diagnosis of an epilepsy syndrome (Rolandic epilepsy with low risk of recurring seizures, Landau-Kleffner syndrome, epileptic encephalopathy with continuous spikes and waves during sleep).

Epilepsy is considered to be resolved for:

- Patients who had an age-dependent epilepsy syndrome but are now past the applicable age, or
- Patients who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Epilepsy is not diagnosed when seizures occur in case of acute injuries of brain structures (strokes, traumas, encephalitis) or metabolism (hypoglycemia, syncope, intoxication) and fever.

2. Epidemiology. Morbidity rate of active epilepsy is similar for the countries with different economic development – 2,3-5,9/1000 for countries with high income economy, 3,7-13,3/1000 for countries with high to moderate income economy, 2,4-22,8/1000 for countries with low to moderate income economy, 3,6-15,4/1000 for countries with low income economy.

Morbidity rate is higher for countries with low income and moderate income economy. The average morbidity rate is 45 per 100 000 inhabitants in countries with high income, and 81,7 in the rest of the countries.

In Bulgaria individuals suffering epilepsy are about 50 000.

In 50 - 60% of the patients, the epilepsy onset occurs earlier than 16 years of age. 2-5% of the children younger than 5 years of age suffer febrile seizures.

II. Epileptic Seizures: Definition, Classification, Clinical and EEG Features

1. Definition. *Epileptic seizures* are episodes of suddenly occurring quantitative and/or qualitative impairment of awareness, sensory, motor, autonomic and mental functions. They are an expression of hypersynchronous discharges of cortex neurons. The clinical expression of epileptic seizures depends on the localization of discharges in the cerebral cortex and their dissemination in the brain.

2. Classification – extended ILAE classification of epileptic seizures of 2016 and 2017. Changes comprise: 1. “Focal” replaces “partial”; 2. Seizures with unknown onset can be also classified; 3. Alterations of awareness are used as a criterion for classification of focal seizures; 4. The following classification terms are rejected: “dyscognitive”, “simple partial”, “complex partial”, “mental”, “secondarily generalized”, “aura”, “convulsions”; 5. The following types of seizures are adopted: focal tonic, clonic, atonic, myoclonic, hypermotor (replaces hyperkinetic), cognitive (replaces mental, refers to special manifestations such as aphasia), emotional (gelastic, dacrystic), epileptic spasms, as well as their bilateral versions; 6. New types of generalized seizures are added: absences with eyelid myoclonia, myoclonic absences, myoclonic-atonic, clonic-tonic-clonic, epileptic spasms. Epileptics spasms may be focal, generalized or unknown; 7. The term “bilateral tonic-clonic” replace “secondarily generalized”.

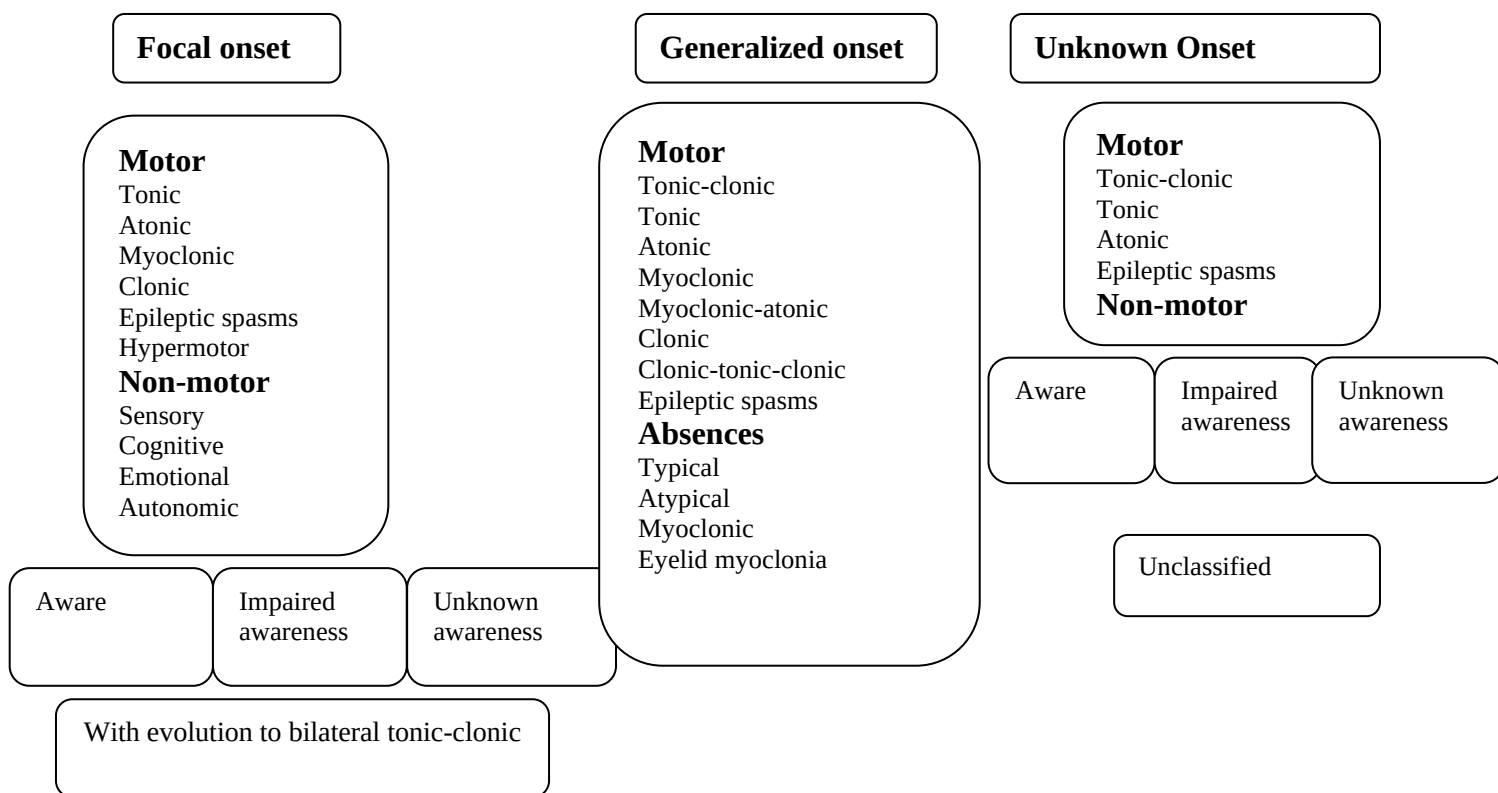


Figure 1. Classification of Types of Epileptic Seizures (2016, 2017)

3. Clinical and EEG Features

In accordance with the EEG and clinical features **epileptic seizures** are characterized as focal (partial) and generalized.

Focal (partial) seizures originate from cortical neuronal networks, rarely from subcortical structures (for example, in case of hypothalamic hamartomas) and stay localized in one of the hemispheres. In some cases, focal seizures are generated in more neuronal networks in both hemispheres (for example, in case of bilateral mesial temporal lobe epilepsy, Rolandic epilepsy). EEG often finds focal finding and signs used for localization of the epileptic focus. The clinical diagnosis is difficult, as only about 40% demonstrate correlation in the scalp EEG during seizure.

- **Focal seizures without awareness impairment** (simple partial seizures) are motor, sensory (including olfactory, gustatory and auditory), autonomic (epigastric aura with nausea, vomiting), versive head and/or eye moving aside, and mental (paroxysmal fear or laugh). They are short and may progress in focal with awareness impairment or bilateral tonic-clonic. *Differential diagnosis:* transitional ischemic attacks, hemi facial spasms and tics.
- **Focal seizures with awareness impairment** (complex partial seizures) occur with awareness alterations and can also progress to bilateral tonic-clonic. Cessation of movements, automatisms and postictal confusion can be seen. In case of focal seizures with awareness impairment originating from the mesial temporal lobes, oroalimentary automatisms (swallowing, munching), other automatisms (for example, arm stereotypes), dystonic phenomena and postictal confusion can be seen. In case of focal seizures with awareness impairment originating from the frontal lobe, expressed motor automatisms such as “bicycle riding”, etc., and quick recovery after seizures are typical. In case of focal seizures with awareness impairment ictal correlation in EEG usually occur. *Differential diagnosis:* In case of non-epileptic seizures, normal alpha rhythm is visualized during the “behavioral alterations and impaired awareness”.

Generalized seizures originate from specific area and excitement quickly spreads along neuronal networks, including cortical and subcortical structures. Generalized seizures may be asymmetric.

- EEG with generalized paroxysmal activity with bilateral synchronous onset
- There is no focal clinic at the onset (only myoclonia may be asymmetric)
- There are different types (refer to the classification of seizures) – absences, myoclonic, clonic, GTCS, tonic, atonic.

Absence seizures are short episodes of impaired awareness (less than 20 sec.), without aura and post-seizure confusion, where no or rare automatisms are observed. Facial automatisms with blinking occur most frequently. They are provoked by hyperventilation or photo stimulation. They start in childhood or adolescence and may continue in adult patients. They often remain unfound in children until the occurrence of generalized tonic-clonic seizure. In case of absence seizures, EEG finds generalized paroxysms of spike-wave complexes 3-3,5 Hz.

Myoclonic seizures are short, asymmetric flickers and movements continuing less than 1 sec. They may be grouped within the frames of a few minutes and may evaluate in clonic seizures. In case of myoclonic seizures, EEG shows quick polyspike - wave complexes.

Clonic seizures are rhythmic motor expressions with or without awareness impairment, which may be of focal origin or may be generalized, simultaneously engaging the upper and lower extremities. EEG finds bilateral rhythmic epileptic discharges.

Tonic seizures are characterized with sudden tonic extension or flexion of the head, body and/or extremities for a few seconds. Usually, they occur in the state of somnolence, while falling asleep or upon awaking. EEG shows discharges with fast activity (sharp waves, spikes) with different amplitude.

Tonic-clonic seizures (grand mal, GTCS) proceed with motor phenomena – generalized tonic stretching of extremities for a few seconds and subsequent rhythmic movements with continuous postictal confusion. They differ from focal seizures with progression to bilateral tonic-clonic due to the lack of aura and focal onset. Ictally, the EEG finds generalized complexes of spikes, or polyspikes and waves, frequently with increased amplitude in the frontal lobes.

Atonic seizures are characterized with short loss of postural tonus, which results in falling and injury. EEG finds generalized polyspike-wave discharge, whereas the EMG verified loss of muscle tonus coincides with the wave. Rarer ictal manifestations have quick activity with different amplitude or discharges of polyspikes and subsequent generalized activity of spike-wave complexes.

III. Etiology and Pathogenesis of Epilepsies

According to **etiology**, epilepsies may be classified as follows: genetic (idiopathic), structural/metabolic, autoimmune, infectious (symptomatic), with unknown etiology (cryptogenic).

1. Genetic (ILAE, 2010) or idiopathic epilepsy is a result of known or supposed genetic defect and the epileptic seizures are the main symptom of the disease. The molecular-genetic investigations are the main diagnostic tests (for example, SCNA1A gene in case of Dravet syndrome). External factors contribute to the expression of the disease. Most of generalized epilepsies, such as infancy and juvenile epilepsy, Dravet syndrome, genetic (generalized) epilepsy with febrile seizures plus (GEFS+) (Tables 1, 3, 4), and some focal epilepsies, such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), autosomal dominant partial epilepsy with auditory features (ADPEAF), etc. (Tables 2, 3, 4), are genetic.

Table 1. Main Genes in Case of Genetic (Mainly Generalized) Epilepsies

	Monogenic disease	Predisposition gene
Autosomal-dominant epileptic syndromes in infancy		
Benign familial neonatal seizures	KCNQ2 KCNQ3	
Benign familial neonatal-infantile seizures	SCN2A	
Febrile seizures, GEFS+ and Dravet syndrome		
GEFS+, febrile seizures, Dravet syndrome	SCN1A	
GEFS+	SCN1B	
GEFS+, febrile seizures, Dravet syndrome	GABRG2	
GEFS+		GABRD

Idiopathic generalized epilepsy		
Childhood absence epilepsy (with febrile seizures)	GABRG2	
Juvenile myoclonic epilepsy	GABRA1	
Different phenotypes	CLCN2	
Childhood absence epilepsy (however: other phenotypes and epileptic syndromes too!)		CACNA1H
Juvenile myoclonic epilepsy (however: other phenotypes and epileptic syndromes too!)		EFHC1

Table 2. Familial Focal Epileptic Syndromes

	Age	Clinical picture	Chromosome, gene
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	10 – 20 r.	Nocturnal hypermotor seizures, often with preserved awareness	CHRNA4 CHRNA2 CHRNA2
Autosomal dominant partial epilepsy with auditory features (ADPEAF)	20 – 40 r.	Auras with auditory dysphasic or visual features	LGI1
Familial mesial temporal lobe epilepsies			
Without HS, without FS	20 – 40 years	Dèjà vu, autonomic or affective aura	4q*
With HS, +/- FS	10 – 30 years	Dèjà vu, autonomic or affective aura	Unknown
FS, without HS	10 – 20 years	Dèjà vu, autonomic aura	18q*, 1q*
Familial occipital temporal lobe epilepsy	10 – 40 years	CPS, migraine, different focal seizures	9q*
Familial partial epilepsy with variable foci (FPEVF)	10 – 30 years	Frontal, temporal, occipital, centroparietal seizures	22q12
Focal epilepsy with pericentral spikes	10 – 20 years	Hemiconvulsions, often nocturnal, other partial seizures	4p15*
* Chromosomic link found in one family only.			

HS= hippocampal sclerosis.

FS= febrile seizures. CPS= complex partial seizures

Table 3. Epileptic Syndromes and Genes

Phenotype (according to the age of manifestation)	Inheritance	Gene
Neonatal period		
Pyridoxamine 5'-phosphate oxidase deficiency (PNPOD)	AR	<i>PNPO</i>
Pyridoxine- dependent epilepsy (EPD)	AR	<i>ALDH7A1</i>
Benign familial neonatal seizures (BFNS)	AD	<i>KCNQ2, KCNQ3</i>
Infancy and childhood		
Familial infantile myoclonic epilepsy (FIME)	AR	<i>TBC1D24</i>
Benign familial infantile seizures (BFIS)	AD	<i>PRRT2, SCN2A, SCN8A</i>
Amish infantile epileptic syndromes (AIES)	AR	<i>ST3GAL5</i>
Early infantile epileptic encephalopathies (EIEE)	AD	<i>CACNA1A, GABRA1, GABRB3, KCNQ2, KCNT1, SCN2A, SCN8A</i>
	AR	<i>AARS, ARV1, DOCK7, FRRS1L, GUF1, ITPA, NECAP1, PLCB1, SLC12A5, SLC13A5, SLC25A12, SLC25A22, ST3GAL3, SZT2, TBC1D24, WWOX</i>
	X-linked, D	<i>CDKL5</i>
	X-linked, R	<i>ARHGEF9</i>
	X	<i>ALG13, PCDH19</i>
	unknown	<i>DNM1, EEF1A2, FGF12, GABRB1, GNAO1, GRIN2B, GRIN2D, HCN1, KCNA2, KCNB1, SIK1, SLC1A2, SPTAN1, STXBP1, UBA5</i>
Dravet Syndrome (DS, SMEI)	AR	<i>SCN1A, SCN9A^b</i>
Familial febrile seizures (FFS)	AD	<i>GABRG2, GPR98, SCN1A, SCN9A</i>
	AR	<i>CPA6</i>
Generalized (genetic) epilepsy with febrile seizures plus (GEFS +)	AR	<i>GABRD, GABRG2, SCN1A, SCN1B, SCN9A, STX1B</i>
Generalized epilepsy and paroxysmal dyskinesia (GEPD)	AD	<i>KCNMA1</i>
Myoclonic-astatic epilepsy (MAE)	AD	<i>SLC6A1</i>
Childhood onset epileptic encephalopathy (COEE)	AD	<i>CHD2</i>
Focal epilepsy with speech disorder (FESD), with or without intellectual disability	AD	<i>GRIN2A</i>
Childhood absence epilepsy (CAE)	AD	<i>GABRG2</i>
	unknown	<i>CACNA1H, GABRA1, GABRB3</i>

Phenotype (according to the age of manifestation)	Inheritance	Gene
Adolescence and adulthood		
Juvenile absence epilepsy (JAE)	AD	<i>CLCN2^a, EFHC1</i>
Juvenile myoclonic epilepsy (JME)	AD	<i>CACNB4, CLCN2^a, EFHC1, GABRD</i>
	unknown	<i>GABRA1</i>
Idiopathic generalized epilepsy (IGE)	AD	<i>CACNB4, CLCN2^a, GABRD, SLC12A5, SLC2A1</i>
	unknown	<i>CACNA1H, CASR</i>
Adult onset familial epilepsy adult myoclonic epilepsy (FAME)	AD	<i>ADRA2B</i>
	AD	<i>CNTN2</i>
Familial temporal lobe epilepsy (FTLE)	AD	<i>CPA6, GAL, LGI1</i>
Unspecified age onset		
Progressive myoclonic epilepsy (PME)	AD	<i>KCNC1</i>
	AR	<i>CERS1, CSTB, EPM2A, GOSR2, KCTD7, LMNB2, NHLRC1, PRDM8, PRICKLE1, SCARB2</i>
Nocturnal front lobe epilepsy (NFLE)	AD	<i>CHRNA2, CHRNA4, KCNT1</i>
	unknown	<i>CHRNA2</i>
Familial focal epilepsy with variable foci (FFEVF)	AR	<i>DEPDC5</i>

Abbreviations: Inheritance: AD- Autosomal dominant; AR- Autosomal recessive; X-linked, R- X-linked recessive inheritance; X-linked, D-X-linked dominant inheritance

Table 4. Epilepsy-Associated Genes (2018)

Genes	Associated epileptic syndromes
ARX	Infantile spasms, early infantile epileptic encephalopathies
ATP1A2	Benign familial neonatal seizures, familial hemiplegic migraine and epilepsy
CACNA1A	Absence epilepsy and episodic ataxia, familial hemiplegic migraine
CACNB4	Juvenile myoclonic epilepsy
CDKL5 (STK9)	Infantile spasms between 3 and 6 months, neuro-mental development disorders, stereotypic movements of arms, atypical hypsarrhythmia (5 times more frequent in girls)
CHRNA4	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNA2	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNA7	Juvenile myoclonic epilepsy
CLCN2	Childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy
CLTC	Epileptic encephalopathy with intellectual disability
DHDDS	Epileptic encephalopathy with intellectual disability

EFHC1	Juvenile myoclonic epilepsy
GABRD	Genetic epilepsy with febrile seizures plus
GABRA1	Juvenile myoclonic epilepsy
GABRB2	Epileptic encephalopathy with intellectual disability
GABRB3	Epilepsy and autism
GABRG2	Childhood absence epilepsy, Genetic epilepsy with febrile seizures plus (GEFS+), Dravet syndrome (SMEI), simple febrile seizures
GABBR2	Epileptic encephalopathy with intellectual disability, Rett syndrome
GNAO1	GNAO1- epileptic encephalopathy and motor disorders
KCNQ2	Benign familial neonatal seizures (KCNQ2-BFNE), neonatal epileptic encephalopathies (KCNQ2-NEE)
KCNQ3	Benign familial neonatal seizures (BFNE), benign familial infantile epilepsy (BFIE), possible KCNQ3-related intellectual deficiency.
KCNMA1	Generalized epilepsy with paroxysmal dyskinesias
KCNT1	Epilepsy of infancy with migrating focal seizures (EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).
LGI1	Autosomal dominant partial epilepsy with auditory features
NTRK2	Temporal lobe epilepsy, epileptic encephalopathy with intellectual disability
NUS1	Epileptic encephalopathy with intellectual disability
PCDH19	Epilepsy of women with intellectual disability
PRRT2	Epilepsy, familial hemiplegic migraine, paroxysmal dyskinesia
RAB11A	Epileptic encephalopathy with intellectual disability
SCN1A	Genetic epilepsy with febrile seizures plus (GEFS+), Dravet syndrome (SMEI), familial hemiplegic migraine (FHM3)
SCN1B	Genetic epilepsy with febrile seizures plus (GEFS+), temporal lobe epilepsy
SCN2A	Genetic epilepsy with febrile seizures plus (GEFS+), early epileptic encephalopathy with neonatal onset or in childhood, benign familial neonatal/ infantile seizures
SCN8A	Early infantile epileptic encephalopathy – 13 (EIEE13 or Ohtahara syndrome), benign familial infantile seizures (BFIS5 with focal to bilateral tonic-clonic, or GTCS up to 2 years of age), paroxysmal dyskinesia
SLC2A1	Early onset absence epilepsy, myoclonic-astatic epilepsy, generalized epilepsy, epileptic encephalopathy with deficiency of glucose transporter type 1 (GLUT1), epilepsy with paroxysmal, exercise-induced dyskinesias
SLC25A22	Early myoclonic encephalopathy, migrating partial seizures in infancy
SLC35A2	Early onset epileptic encephalopathy
SNAP25	Epileptic encephalopathy with intellectual disability
ST3GAL5	Epileptic encephalopathy with severe intellectual disability, choreoathetosis, scoliosis, facial dimorphism, pigmentation disorders

STXBP1	Early infantile epileptic encephalopathy (Ohtahara syndrome, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome (non SCN1A-related), Rett syndrome (non MECP2-related and non CDKL5-mutation related). Focal epilepsy with intellectual deficiency.
TBC1D24	Familial infantile myoclonic epilepsy, focal epilepsy with developmental deficiency, drug-resistant epileptic encephalopathy, including DOORS syndrome (deafness, osteodystrophy, intellectual disability, epileptic seizures), non-syndrome deafness

2. Structural/ metabolic (symptomatic) epilepsy is the epilepsy related to specific factors. Structural lesions are grouped as follows: structural lesions in case of acquired disorders of the CNS (strokes, traumas), with genetic causes (some malformations of the cortical development, tuberous sclerosis) and metabolic causes (for example, epilepsies in case of leukodystrophies, progressive myoclonic epilepsies in case of lysosome accumulation-related diseases, and other metabolic defects):

Epilepsies with symptomatic or “structural/ metabolic” etiology (ILAE, 2010):

- Hippocampal sclerosis
- Tumors –gliomas, DNET, gangliogliomas, oligodendrogliomas
- Malformations of cortical development:
 - Focal cortical dysplasias
 - Hemimegalencephaly
 - Malformations of cortical development with nevi
 - Schizencephaly, lissencephalia, holoprosencephaly
 - Cortical dysplasias
 - Heterotopias
 - Hamartomas
- Cerebrovascular malformations
 - Cavernous angiomas, arteriovenous malformations (AVM)
 - Sturge-Weber syndrome
- Hypoxic-ischemic (local infarctions, diffuse hypoxic-ischemic disorders, periventricular leukomalacia), cerebral hemorrhages, venous thromboses
- Traumas
- Congenital
 - Tuberous sclerosis
 - Progressive myoclonic epilepsies
 - Metabolic syndromes
 - Channelopathies
 - Mitochondrial diseases
 - Chromosomic aberrations

3. **Immune-** in case of immune-mediated irritations of the CNS – vasculitis, autoimmune encephalitis, including Rasmussen encephalitis.

4. **Infectious-** in case of infections of the CNS – meningitis, encephalitis, abscesses.

5. **Epilepsy of unknown cause (*cryptogenic*)** is the epilepsy of unknown cause where genetic defect that is not yet proved is possible. Epilepsies with genetic and unknown etiology represent about 60%, and those with structural/ metabolic etiology – about 40%.

Other types with known etiology are to be adopted in future. Where the structural etiology is genetically substantiated, both terms may be used – structural and genetic (tuberous sclerosis complex).

Pathogenesis. The balance between excitement and depressive processes in neuronal populations with dysfunctions is damaged. Epileptic seizures occur due to excessive and synchronous neuronal activity that is disseminated in neuronal networks, engages different sections of the cerebral cortex and/or subcortical structures and determines the characteristics of the seizures.

IV. Classification of Epilepsies

In 2010 ILAE proposed corrections in the terminology, classification and concepts of epileptic seizures and syndromes determined by the development of the neuro depicting technologies, fundamental studies of epileptogenesis and molecular genetics mechanisms. The concept of generalized and focal seizures does not apply to “electro-clinical” syndromes for which detailed classification by age periods of occurrence is presented.

Classification of epilepsies according to:

1. **Evolution.** According to the 2010 classification, epilepsies are classified as follows:

- self-limiting (for example, idiopathic focal childhood epilepsies, such as Rolandic and benign occipital epilepsies, childhood absence epilepsy in 75-80%). At specific expected age they are characterized with spontaneous remission. There are no cognitive and behavioral disorders, including during the active phase of seizures.

- drug-controlled (for example, juvenile myoclonus epilepsy),

- drug-resistant (for example, Dravet, West, Lennox-Gastaut syndrome), which are defined by:

1. Quantitative assessment of seizure frequency and gravity (awareness disorders, contusions, long postictal dysfunction)
2. Ineffective ASD treatment, adequate for the type of seizures and in adequate doses. According to the last definition proposed by ILAE in 2009, “drug-resistant are patients with failure of adequate trials of two tolerated, appropriately chosen and used ASD, whether as monotherapy or in combination, to achieve sustained seizure freedom (for a period of 1 year or 3 times longer than the longest inter-seizure period during the last year)”. Adequate ASD trail means drug application in appropriate dose and for sufficiently long period of time. Drug-resistant patients are characterized with

significant negative effects of epileptic seizures on the quality of living. In case drug resistance is found, rotational polytherapy needs to be applied with more than 2 ASD, and in case of failed treatment and indications, possibilities for surgical treatment should be discussed.

2. Electric-clinical syndromes according to the onset age:

Neonatal period

- Benign familial neonatal seizures (BFNS)
- Early myoclonic encephalopathy (EME)
- Ohtahara syndromes

Infancy

- Epilepsy of infancy with migrating focal seizures
- West syndrome
- Myoclonic epilepsies in infancy (MEI)
- Benign infantile seizures
- Dravet syndrome (SMEI)
- Myoclonic encephalopathies in case of non-progressive diseases

Childhood

- Febrile seizures plus (FS+)
- Early onset benign occipital epilepsy (Panayotopoulos syndrome)
- Late onset benign occipital epilepsy (Gastaut type)
- Benign epilepsy with centrotemporal spikes (BECTS, Rolandic epilepsy)
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Childhood absence epilepsy
- Epilepsy with myoclonic-atonic seizures (Myoclonic-astatic epilepsy)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome
- Epileptic encephalopathy with continuous spikes and waves during sleep (CSWS), including Landau-Kleffner (LKS) syndrome

Adolescence and adulthood

- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with generalized tonic-clonic seizures
- Progressive myoclonic epilepsies
- Autosomal dominant partial epilepsy with auditory features (ADPEAF)
- Other familial temporal lobe epilepsies

More unspecific age-related

- Familial focal epilepsy with variable foci (childhood/ adulthood)
- Reflex epilepsies

Different

- mesial temporal lobe epilepsy with hippocampal sclerosis
- Rasmussen Syndrome
- Gelastic seizures in case of hippocampal hamartomas

Conditions with epileptic seizures that are not diagnosed as epilepsy.

- Benign neonatal seizures (BNS)
- The new ILAE Classification and Definition of Epileptic Syndromes by Age of Onset, 2022 introduces some terminological changes (Zuberi SM et al. *Epilepsia*. 2022 Jun;63(6):1349-1397; Specchio N. et al. *Epilepsia*. 2022;63(6):1398-1442; Riney K et al. *Epilepsia*. 2022 Jun;63(6):1443-1474. Hirsch E et al. *Epilepsia* 2022;63(6):1475-1499). Only Dravet syndrome, Lennox-Gastaut syndrome and Rasmussen syndrome remain with names. West Syndrome becomes Epileptic Infantile Spasm Syndrome; Benign childhood focal epilepsies become self-limiting epilepsies: Idiopathic focal epilepsy with centrotemporal spikes (Roland's) becomes Self-limiting epilepsy with centrotemporal spikes; Panayiotopoulos syndrome (Benign early-onset occipital epilepsy) becomes a self-limiting syndrome with autonomic dysfunction; Gastaut syndrome (Benign late-onset occipital epilepsy) becomes Childhood occipital visual epilepsy; Photosensitive occipital tardive epilepsy. The new change in terminology classifies epilepsies into the following groups according to age of onset (2022):

A. Epilepsies and syndromes in the neonatal period and early age (Zuberi SM, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia*. 2022 Jun;63 (6):1349-1397).

I. Self-limiting epilepsies

1. Self-limited neonatal epilepsies
2. Self-limited familial neonatal epilepsies
3. Self-limited infantile epilepsies
4. Generalized epilepsy with febrile seizures plus (GEFS+)

II. Etiologically specific syndromes

1. KCNQ2- developmental encephalopathies/epileptic encephalopathies
2. Pyridoxine-related developmental encephalopathies/epileptic encephalopathies
3. Pyridocamine-5 phosphatase deficiency – developmental encephalopathies/ epileptic encephalopathies
4. CDKL
5. Developmental encephalopathies/epileptic encephalopathies

6. PCDH19 epilepsy
7. Glucose transporter 1 deficiency syndrome (GLUT 1 DS)
8. Sturge-Weber syndrome
9. Gelastic seizures in hypothalamic hamartomas

III. Developmental encephalopathies and epileptic encephalopathies

1. Early infantile developmental encephalopathies and epileptic encephalopathies
2. Epilepsy in infancy with migrating focal seizures
3. Syndrome with epileptic infantile spasms
4. Dravet syndrome.

B. Epilepsies and syndromes in childhood (Specchio N, et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. *Epilepsia*. 2022 63(6): 1398-1442)

I. Self-limiting epilepsies:

1. Self-limited epilepsy with centrotemporal spikes
2. Self-limited epilepsy with autonomic seizures
3. Childhood occipital visual epilepsy
4. Photosensitive occipital lobe epilepsy

II. Generalized epilepsies:

1. Childhood absence epilepsy
2. Epilepsy with myoclonic absences
3. Epilepsy with myoclonus of the eyelids

III. Epileptic encephalopathies or developmental encephalopathies

1. Epilepsy with myoclonic-atonic seizures
2. Lennox–Gastaut syndrome
3. Epileptic encephalopathies or developmental encephalopathies with a blade - slow wave activation in sleep, Landau Kleffner syndrome, atypical benign partial (focal) epilepsy in childhood
4. Hemiconvulsion - hemiplegia syndrome
5. Epileptic syndrome associated with febrile infections (acute encephalitis with refractory, recurrent focal seizures, or progressive encephalopathy in school-age children)

C. Epilepsies and syndromes with onset at a variable age (Riney K, al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia*. 2022; 63 (6):1443-1474).

I. Generalized epilepsies with polygenic etiology:

1. Juvenile absence epilepsy
2. Juvenile myoclonic epilepsy

3. Epilepsy with GTCP

II. Self-limiting focal epileptic syndromes with complex transmission:

1. Childhood occipital visual epilepsy
2. Photosensitive occipital lobe epilepsy.

III. Focal epilepsies with genetic, structural or genetic-structural etiology

1. Sleep-related hypermotor (hyperkinetic) epilepsy-KCNT1
2. Familial mesial temporal lobe epilepsy
3. Familial focal epilepsy with variable foci
4. Epilepsy with auditory manifestations

IV. Combined generalized and focal epileptic syndromes of polygenic etiology, epilepsy with inducible reading seizures

V. Epileptic encephalopathies

1. Epileptic syndromes with developmental encephalopathies, epileptic encephalopathies, or both;
2. Epileptic syndromes with progressive neurological damage.
3. Progressive myoclonic epilepsy
4. Febrile-infectious-related epileptic syndromes (FIRES)

3. According to the type of seizures – focal, generalized and generalized and focal epilepsy.

The 2010 classification of epileptic seizures and epilepsies repeals the terms “focal and generalized epilepsy”, however most of the patients at the age of 12+ do not electro-clinical syndrome who actually are the patients with “partial epilepsy” according to the previous classification. With the 2014 revision the classification recognizes the terms “focal and generalized epilepsy” as a good description in cases where electro-clinical syndrome cannot be defined. In 2016 the type of “generalized and focal epilepsy” is added for the cases with focal and generalized seizures, as well as unknown – in case of inability to determine the type of seizures.

4. According to etiology – refer to Section III. Etiology

5. Main epilepsies and epileptic syndromes. Epilepsies/ epileptic syndromes are diseases of similar type of clinical manifestations and with common pathogenesis, forecast and treatment response. According to the type of epileptic seizures, the age onset, development, neurological status, provoking factors, etiology, gravity, family history, relations with sleep, EEG and forecasts, they are characterized as: focal (partial), generalized, reflex epilepsies, epileptic encephalopathies and conditions that do not require the epilepsy diagnosis.

1. Focal (Partial) Epilepsies

Self-limited epilepsy with centrotemporal spikes (Rolandic epilepsy or benign childhood focal epilepsy with centrotemporal spikes, BECTS)

- Onset 3-15 years of age
- Frequency - 10-11/100 000 inhabitants
- Clinical description: partial seizures with “Silvia” localization affecting the face, oropharynx, arm (cessation of speech, clonic flickers, paresthesia, increased salivation). Secondly generalized tonic-clonic seizures (SGTCS). Normal neurological status and intellect.
- EEG – unilateral or bilateral focal centrotemporal spikes increasing during sleep.
- Treatment: Good therapeutic control - CBZ, OxCBZ, VPA, LEV, LCM, LTG, BRV, CLZ, ESL.
- Forecast – good.

Genetic (idiopathic) occipital epilepsies. Onset – 1-14 years of age. Normal neurological status and intellect. Epileptic seizures are versive, oculoclonic, hemiclonic, GTCS and complex partial. Two individual age-determined syndromes are differentiated – childhood epilepsy with occipital paroxysms and early onset (Panayotopoulos syndrome) and with late onset - childhood occipital visual epilepsy (Gastaut type).

Self-limiting epilepsy with autonomic seizures (Childhood epilepsy with occipital paroxysms and early onset or Panayotopoulos syndrome).

- Onset –3-6 years of age
- Frequency: 6% of children under 13 with single seizures mainly during sleep. In about 50% occipital paroxysms are found in the EEG.
- Clinical description: Rare epileptic seizures, mainly during sleep (66%), with duration of 5-10 minutes up to autonomic status (40%), awareness – up to 80-90% impaired in the course of the seizure. Seizures have aversive onset (80%), autonomic manifestations – vomiting or cough only, feeling sick (60%), reddening/ growing pale, incontinence, mydriasis, convulsions, hemiconvulsions or GTCS. Possible ictal syncope. Visual features (up to 7%).
- EEG: Interictal – functional multifocal spike-wave complexes (90%); occipital paroxysms or spikes, which disappear at about 13 years of age (75%), extraoccipital spikes, normal EEG, generalized discharges. Ictal EEG – most often rhythmic slow wave activity.
- Treatment: CBZ, OxCBZ, VPA, LCM.
- Forecast – good.

Childhood occipital visual epilepsy (Childhood epilepsy with occipital paroxysms and late onset – Gastaut type)

- Onset: after 8 years of age
- Clinical description: frequent partial seizures while awake going with: visual symptoms – elementary visual features (stereotypic colors, circles) 5-10 s up to 1-2 minutes, visual illusions (micropsia, metamorphopsia), hallucinations (10%) and blindness. Non-visual symptoms – sight aversion, possibly head aversion (25%), syndromes from propagation to excitement (more rarely) –

hemiclonic (43%), complex partial seizures (14%), GTCS (13%). Postictal headache – diffuse, acute, sometimes non-different from migraine, and in 10% of the patients – nausea and vomiting.

- EEG: Interictal EEG – occipital paroxysms upon eye closing (EC). Ictal EEG – quick occipital spikes, with progressive delay and high voltage.
 - Лечение: CBZ, ОxCBZ, VPA, LCM, BRV, ESL
- Forecast: relatively good, remissions after 2-4 years in 60% of the patients.

Symptomatic focal epilepsies (temporal lobe, frontal lobe, parietal lobe, occipital lobe epilepsy)

Temporal lobe epilepsy

- Onset in childhood.
- The main causes are tumors (DNET, gangliogliomas), encephalitis, mesial temporal sclerosis, dysplasia, and traumas. They are medial (mesial) epilepsies in 75% (in case of hippocampal sclerosis or another etiology found by means of MRI) and lateral (neocortical) in 25%. Medical history for febrile seizures is frequent.
- Clinical description: Main types of seizures are simple and complex partial with or without secondary generalization and (significant) postictal confusion. In case of mesial localization there are epigastric sensations, autonomic dysfunction, psychosensory sensations (dèjà vu, jamais vu), odorous and gustatory hallucinations, visual phenomena, motor orofacial automatisms, vocalizations. In case of lateral (neocortical) localization, sensory aphasia, vomiting and auditory symptoms are manifested. There is therapeutic resistance. Upon data for mesial temporal sclerosis or another lesion etiology, operative treatment should be discussed.

Frontal lobe epilepsies

- Clinical description: Seizures are simple, complex partial and SGTCS mainly during sleep. Frontal seizures are short with minimum postictal confusion, with quick secondary generalization, expressed motor manifestation (tonic, postural), mimic automatisms, frequent falling in case of bilateral discharges. Seizures from the motor cortex are simple focal motor in one part of the body with subsequent irradiation, myoclonic, epilepsy partialis continua and Todd's postictal paresis. Seizures from the additional motor cortex are hypermotor, asymmetric movements of extremities, pelvis, shoulders, head, sight aversion, vocalization, speech cessation and rhythmic stereotypes of extremities.

Parietal lobe epilepsies are characterized with simple partial sensory (with pain, paresthesia), or motor seizures with or without secondary generalization, Todd's ictal and postictal paresis.

Occipital lobe epilepsies are caused by cortical dysplasia, vascular malformations, hypoxic-ischemic encephalopathy, tumors and celiac disease.

- Clinical description: Seizures are simple partial with vision symptoms (exciting, rarely – hallucinations, ictal blindness, hemianopsia) , SGTCS, contralateral aversion of sight and nystagmus, blinking, ictal or postictal headache.

- **Treatment of symptomatic focal epilepsies:** VPA, CBZ, OxCBZ, LTG, LEV, TPM, LCM, BRV, ESL and surgical treatment.

Rasmussen Encephalitis

- Onset - 14 months – 14 years
- Etiology and pathogenesis – immune-mediated epileptic encephalopathy (availability of antibodies to the GluR3 subunit of the glutamate receptors, anti-GluR ϵ 2 and anti-Munc18-11 in some patients).
- Histopathology – glial nodules, perivascular lymphoid infiltrations.
- Drug-resistant focal seizures, epilepsy partialis continua (60%), progressive hemiparesis;
- Progressive intellectual deficiency.
- *CT and MRI* - progressive cerebral hemiatrophy.
- EEG- polymorphic delta activity, disappearance of the normal main activity, frequent epileptiform discharges that are predominantly unilateral and may be periodic.
- Treatment: ASM, i.v. IgG and plasmapheresis with temporary success. Surgical treatment (functional hemispherectomy) is a method of choice.

Hemiconvulsion-hemiplegia-epilepsy syndrome (HHE)

- Etiology comprises infections of the CNS (Herpes simplex-encephalitis) or brain stroke.
- Onset between 5 months and 4 years (91%).
- Clinic: I stage - HH syndrome (hemiconvulsion-hemiplegia). II stage – HHE (hemiconvulsion-hemiplegia-epilepsy) syndrome in 80% after HH.
- Diagnosis: cerebrospinal fluid examination, CT, MRI (edematous hemisphere with subsequent hemiatrophy).
- Status epilepticus treatment, VPA, CBZ, OxCBZ, LTG, LEV, TPM, LCM, BRV, ESL, surgical treatment.
- Forecast: hemiparesis, aphasia, drug-resistant partial epilepsy.

2. Genetic (Idiopathic) Epilepsies

Childhood absence epilepsy

- Genetic predisposition (multifactorial).
- Onset between 3 to 10 years.
- Clinical description: typical absences, most often with eyelid myoclonia, recurring on daily basis. Absences are often activated by photo stimulation and hyperventilation. More than 50% of patients during adolescence also suffer GTCS.

- EEG - ictal generalized bilaterally synchronous paroxysms from symmetric spike-wave complexes with frequency of 2 to 4 Hz. Normal main activity.
- Treatment - VPA, ESM, LTG, Clonazepam. Possible exacerbation as a result of CBZ, GBP, OxCBZ, PHT, TGB and VGB, therefore they should not be applied.
- Forecast – good, they disappear at the age of about 20 years. More unfavorable forecast refers to onset before 4 years and above 9 years of age where GTCS also exist (20%-60%).

Juvenile absence epilepsy

- Genetic predisposition.
- Onset at about puberty, adolescence.
- Clinical description: Absences which are rarer than in childhood absence epilepsy. About 80% of patients also suffer GTCS, or GTCS occur before the absence manifestation.
- EEG- generalized spike-wave complexes.
- Treatment - VPA, ESM, LTG, Clonazepam. Possible exacerbation as a result of CBZ, GBP, OxCBZ, PHT, TGB and VGB, therefore they should not be applied.
- Forecast: Good follow-up with therapy. This epilepsy may become juvenile myoclonic epilepsy.

Juvenile myoclonic epilepsy – the most common primarily generalized epilepsy (morbidity rate 1-3/1000).

- Family history in about 40%. Autosomal-recessive, autosomal dominant inheritance.
- Onset between 8 and 18 years of age, most often at about 15 years of age.
- Clinical description: Myoclonic seizures, GTCS, clonic, absences, most often early in the morning, after sleep or during the night. Absent status epilepticus. Provoking factors – sleep deprivation, photosensitivity, alcohol.
- EEG: generalized paroxysms spike-wave and polyspike-wave 4-6 Hz in case of normal main activity, and 50% - focal abnormality or asymmetry too.
- Differential diagnosis: myoclonic-astatic epilepsy has earlier onset. Progressive myoclonic epilepsies with different causes – in case of diseases with accumulation in lysosomes (most often, ceroid lipofuscinosis), in case of mitochondrial diseases, in case of Lafora and Unverricht-Lundborg diseases.
- Treatment: VPA, Clonazepam, LEV, LTG, TPM. Possible exacerbation as a result of VGB, TGB, CBZ, OxCBZ, PHT, GBP, PGB, therefore they should not be applied.
- Forecast – upon termination of treatment recurrence is found in about 90%.

Epilepsy with GTCS upon wake-up.

- Onset – 9 – 24 years of age, frequency 22-37% of IGE.

- GTCS are the main type of seizures occurring up to 2 hours after wake-up, however absences and myoclonic seizures are also possible.
- EEG – disorganized main activity and generalized paroxysms of spike-wave complexes.

Myoclonic-astatic epilepsy (Doose syndrome).

- Onset at the age of 2 to 5 years in children with normal development. Mutations in Na⁺ channels SCN1A, SCN2A and SCN1B subunits are rarely found.
- Clinical description: The myoclonic-astatic seizures are the main type of seizures, however absences, myoclonic, atonic, non-convulsive absence status, GTCS, and very rarely – tonic seizures, are also possible.
- EEG with normal main activity and discharges of polyspike-wave complexes.
- Differential diagnosis: Benign myoclonic infancy epilepsy, Dravet syndrome (SMEI), cryptogenic syndrome of Lennox-Gastaut (myoclonic version), progressive myoclonic epilepsies in MERRF, Lafora, Unverricht-Lundborg diseases, leukodystrophies (progressive neurological deficiency and progressive atrophy in MRI and CT, metabolic defect found), atypical benign partial epilepsies in childhood (Rolandic and Panayotopoulos type) where drop-attacks are possible in atypical absences and negative myoclonus.
- Treatment: VPA, ESM, benzodiazepines, TPM, LEV, low doses of LTG, bromides, corticosteroids. Exacerbation as a result of CBZ, VGB, PHT is typical.
- Forecast – unfavorable in 50% due to drug-resistant seizures, cognitive deficiency, behavioral deviations.

Epilepsy with myoclonic absences

- Rare epilepsy (0,5-1%) with onset between 5 months to 13 years of age, at 7 years of age on average.
- Clinical description: Myoclonia (perioral, of arms, shoulders, including asymmetric (8-60/s); GTCS, atonic, absence status. They are provoked by HV, photostimulation.
- EEG with short generalized, focal and multifocal spike-wave complexes or polyspike-wave with frequency of 3 Hz.
- Forecast: drug-resistance is often seen, cognitive deficiency, transition to juvenile myoclonic epilepsy.

Benign neonatal seizures

- In some cases, they are familial, with autosomal dominant inheritance.
- Onset - 2-3 days after birth giving.
- Clinical description: Partial epileptic syndrome – short seizures.

- Normal neurological status.
- EEG- not specific.
- Forecast – good.

Progressive myoclonic epilepsies

- Varied etiology – diseases with accumulation in lysosomes (most often ceroid lipofuscinosis), mitochondrial diseases, Unverricht-Lundborg disease, Lafora disease.
- Clinical description: Myoclonia, epileptic seizures. Progressive neurological deficiency.
- Forecast - unfavorable.

3. Reflex Epilepsies

They go with reflex seizures (generalized, myoclonic or focal) provoked by specific afferent stimuli: *external* (blinking lights, tactile, reading, eating) and *internal* (movements, thinking, music, calculus, decision making). Photogenic seizures are most common.

1. Genetic (idiopathic) photosensitive occipital epilepsy and other visually induced epilepsies. Upon intermittent photo stimulation (IPS) or another light stimulation (video games, self-induction while blinking or movements in front of the eyes) photoparoxysmal response (PPR) is generated – focal or generalized spike/ polyspike-wave paroxysms. Photogenic seizures occur in 5 to 10% of patients suffering epilepsy under 18 years of age. 42% of all patients with PPR *pure photogenic epilepsy* (only photogenic seizures), 40% have spontaneous and photogenic induced seizures, and 18% - only spontaneous seizures. *Generalized epilepsies with expressed PPR* comprise childhood absences, juvenile absence epilepsy, juvenile myoclonic epilepsy and epilepsy with GTCS upon wake-up, epilepsy with eyelid myoclonia and absences (Jeavons syndrome) and SMEI.

Genetic (idiopathic) photosensitive occipital epilepsy is an age-dependent syndrome in children with occipital epileptogenicity due to blinking lights – video games, TV, disco club, and children with idiopathic partial or generalized epilepsy with occipital seizures.

Clinic – PS-induced occipital seizures – autonomic symptoms (vomiting, like in Panayotopoulos syndrome), SGTCS, GTCS.

EEG – Interictal: PPR upon PS – occipital or generalized paroxysms. *Ictal EEG* – occipital paroxysms with temporal propagation.

2. Startle epilepsy - in children with neurological and intellectual deficiency and other types of seizures where seizures occur upon startling, most frequently due to high noise. DD - Hyperekplexia (Startle disease)

3. Reading epilepsy - manifested with myoclonic seizures in the oral, perioral, masseteric muscles while reading.

4. Epileptic encephalopathies and developmental encephalopathies - etiology - structural/metabolic and genetic causes (Table 5) (Specchio N, Curatolo P. Developmental and epileptic encephalopathies: what we do and do not know. Brain. 2021;144(1): 32-43).

Developmental encephalopathies: Characterized by:

- Delayed neuropsychological development or intellectual deficit due to non-progressive brain damage, combined or not with epilepsy;
- Neurocognitive and behavioral deficits persist regardless of epilepsy control

Epileptic encephalopathies - early infantile (Ohtahara syndrome, West, migrating focal seizures, Dravet syndrome) and with late onset: Lennox-Gastaut syndrome.

- Continuous epileptic activity or frequent epileptic seizures cause cognitive regression;
- Neurocognitive and behavioral abnormalities may improve with seizure control reduction of interictal epileptic activity

Developmental Encephalopathies and Epileptic Encephalopathies - cognition and behavior are impaired regardless of the onset of epilepsy, which is of high frequency and with epileptiform activity;

- Cognitive and behavioral impairments remain, even when seizures are controlled; there may be some improvement

Table 5. Developmental encephalopathies and epileptic encephalopathies - most common gene defects

Gene	Protein	Seizure type	Syndrome	DEE characteristic	ASD response
CDKL5	Kinase	Spasms, myoclonus Tonic, tonic-clonic	CDD	Mental deficiency, motor deficiency	Resistant
SCN1A	Na ⁺ channel: Nav1.1	Distinct, typical GTCP in To	Dravet, GEFS+, early infantile EE (West)	Dravet , mental deficiency, delayed NPR	Na⁺ channel agonists-worse
KCNQ2 /KCNQ3	K ⁺ channels: K _v 7.2, K _v 7.3	Various Typical focal to VGTCP	Ohtahara-, BFNE	Mental deficiency	Variable ± response to Retigabine

PCDH19	Protocadherin 19	Focal, provocation by To		Mental deficiency, ASD	
SCN2A	Na ⁺ channel: Na _v 1.2	Various-, focal, myoclonic, atonic	West, Ohtahara, Lennox-Gastaut, rare BFNE	Mental deficiency, delayed NPR, ASD	Na⁺ channel antagonists improve or worsen
SCN8A	Na ⁺ channel: Na _v 1.6	Various focal, GTCP, spasms, myoclonus, absences	West, Lennox-Gastaut, etc.	Mental deficiency, delayed NPR	Response to Na⁺ channel antagonists

Syndrome with epileptic infantile spasms (West syndrome)

- Onset – during the first year, most frequently at the age of 3 to 5 months. Frequency 2-4/100 000.
- Etiology - cryptogenic in 30%, symptomatic in about 70% (degenerative, dysmetabolic disorders, cortical dysplasia, tuberous sclerosis, hypoxic-ischemic encephalopathy, cerebral hemorrhages, infections, traumas, etc.).
- Damaged neural-mental development in 75% at the onset (mental and neurological deficiency).
- Epileptic seizures – epileptic (infantile) spasms, most frequently of flexion type affecting the axial muscles.
- EEG – hypsarrhythmia, disorientated, with bilateral asynchronous high voltage waves, multifocal epileptic discharges mainly in the posterior cerebral areas, voltage depression during sleep.
- Treatment - ACTH, Vigabatrin. Alternative - VPA, Nitrazepam, Topiramate, ZNS. In case of hemispheric lesions, lobar or smaller malformations of cortical development, proven (through video-EEG and anatomical-clinical-EEG correlations) leading to the clinical manifestation of spasms with (hemi-)hypsarrhythmia, surgery with resection of the lesions is also applied.
- Forecast – unfavorable: high mortality rate (5%), transition to Lennox-Gastaut syndrome or focal epilepsy (25%-65%), cognitive deficiency (66%), motor deficiency. Only 15%-30% of cryptogenic/ idiopathic cases have normal development.

Lennox-Gastaut Syndrome (LGS)

- 1-2% of all epilepsies
- 5-10% of childhood epilepsies.

- Onset – most frequently between 2 and 7 years of age (range of 1-14 years of age)
- About 30%-50% of children with West's s-m progress to LGS
- About 70% to 80% are symptomatic - brain malformations / Lissencephaly, band-shaped heterotopia (Double cortex syndrome), bilateral perisylvian polymicrogyria, tuberous sclerosis, agenesis of the corpus callosum, posthypoxic encephalopathy, postencephalitic encephalopathy/. Idiopathic is up to 20% de novo mutations: CHD2, FOXP1, SCN1A, SCN8A, STXBP1, ALG13, DNMT1, GABRB3, IQSEC2 (Xp11.22)
- Typical LGS criteria are as follows: 1. Polymorphic, therapy resistant seizures – tonic, atonic, atypical absences (2 of 3 types). Epileptic spasms are also possible after West syndrome, GTCP, simple focal and myoclonic seizures. 2. EEG with generalized discharges of spike-wave slow complexes (< 3 Hz) while awake and generalized quick rhythms (≥ 10 Hz) while asleep. 3. Damaged intellectual functions – cognitive, behavior.
- Treatment. No complete follow-up of seizures is possible. The first choice of ASD comprises VPA, LTG, TPM, alternative - ESM, LEV, CBZ, PB, Phenytoin (PHT), Clonazepam, Rufinamide, ZNS, Cannabidiol in combination with Clobazam, Fenfluramine according to the prevailing seizures for the time being; ACTH/ corticosteroid courses. In LGS, surgery with resection of lesions, callosotomy and vagus nerve stimulation is also applied for frequent and traumatic drop attacks.
- Forecast – unfavorable: high mortality rate (5%), intellectual deficiency in 85-95% and persistence of seizures in 78% to 96%. Nocturnal tonic seizures are most frequent after puberty.

Severe early childhood myoclonic epilepsy (Dravet syndrome, SMEI)

- 1% of epilepsies in childhood, in about 80% of cases mutations in SCN1A, SCN1B, PCDH19, GABRA1, STXBP1 are found.
- Normal initial neural-mental development.
- Epileptic syndrome – progressive, polymorphic, drug resistant. It begins with complicated febrile seizures after the age of 6 and is supplemented by the following 4 typical kinds of seizures: 1. Generalized seizures – tonic-clonic, clonic and asymmetric tonic, clonic and hemiclonic. 2 Myoclonic seizures (80%) starting at the age of 1 to 5 years. 3. Atypical absences (40%) starting at the age of 1 to 12 years. 4. Complex partial seizures (46%) and SGTCS between 4 months and 4 years of age. Convulsive, myoclonic or absence status epilepticus (SE) occurs frequently.
- Seizures are provoked by t° , photo stimulation, eye movements.
- Cognition (100%) and motor development (20-60%) regress 1-2 years after the onset of the disease.
- Forecast - high mortality up to 3 years and up to 6 years in epi status, sudden unexpected death in epilepsy (SUDEP).

- Treatment: VPA, Clonazepam, Nitrazepam, ESM, Phenobarbital (PB), LEV, bromides, Stiripentol, Cannabidiol in combination with Clobazam, Fenfluramine. CBZ, OxCBZ, PHT, GBP, VGB, TGB, PGB and high dose of LTG exasperate the epileptic seizures and should be therefore not applied.

Epileptic encephalopathy with CSWS or electric status during slow-wave sleep (ESES)

Onset from 1 and 10 years of age, peak – 4-5 years of age

- Description: EEG with continuous peak-wave complexes during slow-wave sleep (CSWS) that take more than 85% of the sleeping time. Polymorphic epileptic seizures. Neuropsychological regress – attention deficiency, hyperactivity, aggressiveness, orofacial apraxia.
- Clinic: 1/3 of the patients have abnormal neurological status, and more than 50% - with MRI pathology.

Development stages:

- 1. Rare nocturnal motor hemiclonic seizures; 2. CSWS, increase and change of the type of epileptic seizures (*nocturnal* motor and GTCS, *daily* typical and atypical absences, myoclonic, clonic, orofacial), cognitive and behavioral deviations. 3. Rare nocturnal GTCS, daily atonic. 4. Improvement, including in EEG (2-7 years of age), with residual defect.
- Diagnosis: EEG during sleep with CSWS – spike-wave complexes with index > 85%. In awake condition – frontal and temporal foci, atypical absences.
- Treatment: VPA, benzodiazepines (clobazam, etc.), LTG, LEV, TPM (CBZ and PHT exasperate), ACTH (80 E/ daily) or prednisone 2-5 mg/kg with reduction for 3 months. In congenital or early, usually hemispheric or lobar lesions with the appearance of CSWS, after proving anatomic-clinical-EEG correlation, surgical disconnective or resective surgery is also applied in certain cases.
- Forecast – it depends on the age at the onset, duration of CSWS, duration and gravity of cognitive damage, response to the AED treatment.

Landau-Kleffner syndrome (acquired aphasia-epilepsy)

- Onset – between 2 and 8 years of age.
- Clinical description: Aphasia (progressive or fluctuating in 100%), epileptic syndrome (75%) – GTCS, focal simple or complex, atypical absences and SGTCS, behavioral deviations (75%) – hyperactivity, aggressiveness, psychosis.
- EEG – focal abnormality with temporal (most often in the dominant hemisphere) and more rarely parietal-occipital localization of spikes, spike-wave complexes, multifocal or *generalized* (mainly during sleep), with possible manifestation of CSWS, which determines the forecast for cognition and intellect.

- Treatment: VPA, ESM, Clobazam, LTG, LEV, TPM, Sulthiam, BRV, ESL. ACTH or corticosteroids with initially high doses – 3 months, which determines the forecast.
- Forecast from benign childhood epilepsy to epileptic encephalopathy. More favorable forecast – in case of aphasia onset after the age of 5, short-term aphasic episodes, quick EEG improvement.

5. Febrile Seizures

Age-related disease with epileptic seizures in infancy and early childhood, with temperature exceeding 38°C, without data for infection of the CNS (meningitis, encephalitis), metabolic disorders, intoxications, etc., which do not require the diagnosis of epilepsy.

- FS are manifested with high temperature which in 85-90% of the cases is caused by infections of the upper and lower respiratory tract (otitis media and acute tonsillitis), varicella, other non-specific viral infections, uroinfections, after vaccinations (85-90% of the cases).
- FS are convulsive, mainly generalized seizures (GTCS in 80% or tonic in 13%), unilateral (4%), and about 3-5% are non-convulsive, characterized with eye deviation, atony, and cyanosis only.
- “Simple” FS (70%) are short (less than 5 minutes), generalized and single for 24 hours.
- Complicated” or “complex” FS (30%) continue more than 15 minutes, focality and/or residual paresis is found, or are ≥ 2 for 24 hours. They require the following investigations – CT, MRI, EEG, and therapy with anti-seizure drugs (ASD). In case of continuous FS, MRI may find acute hippocampal disorder and subsequent progressive atrophy and sclerosis.
- The risk of FS is 30% higher in case of 1st or 2nd degree relatives suffering FS. Retarded motor development and relatives with retarded development.
- The risk of recurrence after first FS is 30% - 40% in children with FS < 18 months, family history of FS and t° during initial seizures <40° C.
- The risk of epilepsy after simple FS is 1% - 2,4%, and after complicated – 4,1% - 6%.

Table 6. Differential Diagnosis in Case of Febrile Seizure

Febrile seizures	
Infection of the CNS – meningitis, encephalitis/ encephalopathy:	
•	Influenza virus-associated encephalitis/ encephalopathy
•	Reye syndrome with encephalopathy
•	Acute encephalitis with febrile seizure status epilepticus
•	Acute encephalitis with refractory, repeated partial seizures
Epilepsy:	
•	Dravet syndrome (SMEI)
•	Generalized epilepsy with febrile seizures + (GEFS+)

• Frontal lobe epilepsy with febrile seizures +
Stroke
Dehydration
Convulsions in case of gastroenteritis

V. Status Epilepticus (SE)

Modern definition and classification of status epilepticus (2015)

SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1). It is a condition, which can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

This definition has 2 dimensions:

1. Length of the seizure and the time point t_1 , beyond which the seizure should be regarded as “abnormally prolonged”. This is the time point when treatment needs to be considered and initiated.
2. The time point after which there is a great risk of long-term consequences (t_2). This is the time point for deciding how aggressive the treatment should be for the purposes of avoiding long-term consequences.

t_1 and t_2 for some types of seizures are determined on the basis of experimental models with animals for cerebral injury.

Table 7. Time Intervals t_1 and t_2 for Different Types of SE

Type of SE	Time interval t_1	Time interval t_2
Tonic-clonic	5 min.	30 min.
Focal with impaired awareness	10 min.	> 60 min.
Absent	10-15 min. (possible changes in future – limited data)	Unknown

SE is most frequent up to 5 years of age and after 65 years of age. In 1/3 of cases, it occurs in case of epilepsy (treatment errors, sudden termination of treatment, intercurrent diseases, etc.), in 1/3 of cases, it is acute symptomatic (in the course of brain stroke, anoxia, cranial trauma, infection of the CNS, metabolic disorders, alcohol abstinence, tumor, medication intoxication), and in 1/3 of cases, causes remain unknown. In case of convulsive SE continuing for more than 30 minutes, CNS injuries occur (vasodilatation, injured blood-brain barrier, increased intracranial pressure, cerebral edema, neuronal death). In case of duration exceeding 60 minutes, SE is considered refractory, and in case of

duration exceeding 24 hours – super refractory. In case of refractory and super refractory SE mortality rate is 32%.

4 diagnostic axes for classification of SE are proposed:

- 1. Semiology**
- 2. Etiology**
- 3. EEG correlates**
- 4. Age**

Every patient should be classified according to all axes. Practically, this is rarely possible due to insufficient data, inability to perform EEG at the beginning of the SE, or due to the dynamics of the SE and the EEG finding.

1. Semiology diagnostic axis

This diagnostic axis refers to clinical manifestations of SE and is the main classification axis. 2 taxonomic criteria are adopted:

1. Existence or absence of visible motor symptoms
2. Degree of awareness impairment (quantitative or qualitative).

Base on these 2 criteria, SE may be:

- **Convulsive** SE – in case of expressed motor symptoms
- **Non-convulsive** SE – in case of no motor symptoms

Modern classification of SE (semiology)

(A) With visible motor symptoms

A.1 Convulsive SE (synonym: tonic-clonic SE)

- A.1.a. Generalized convulsive
- A.1.b. SE with focal onset evolving to bilateral convulsive SE
- A.1.c. Unspecified as focal or generalized
- A.2. Myoclonic SE (with visible epileptic myoclonic seizures)

A.2.a. With coma

A.2.b. Without coma

A.3. Focal motor SE

- A.3.a. Recurring focal motor seizures (Jackson)
- A.3.b. Epilepsia partialis continua
- A.3.c. Aversive status
- A.3.d. Oculoclonic status

- A.3.e. Ictal paresis (focal inhibitory SE)

A.4. Tonic SE

A.5. Hyperkinetic SE

(B) Without visible motor symptoms (non-convulsive SE)

B.1. **With coma** (including the so called difficult to find SE)

B.2. **Without coma**

B.2.a. Generalized SE

B.2.a.a. Typical absent SE

B.2.a.b. Atypical absent SE

B.2.a.c. Myoclonic absent SE

B.2.b. Focal SE

B.2.b.a. Without awareness impairment (aura continua, with autonomic, sensory, visual, odorous, gustatory, psychic, auditory symptoms)

B.2.b.b. Aphasic status

B.2.b.c. With impaired awareness

B.2.c. Unspecified as focal or generalized

B.2.c.a. Autonomic SE

2. Etiology diagnostic axis

Modern classification of SE (etiology)

- Acute SE (stroke, intoxication, encephalitis, etc.)
- SE related to a disease suffered in the past (brain trauma, encephalitis, stroke)
- Progressive SE (brain tumor, Lafora disease, dementias)
- SE in case of specified electro-clinical syndromes (West, Lennox-Gastaut, Landau-Kleffner, Ohtahara, Dravet syndromes, juvenile myoclonus epilepsy, etc.)
- SE with unknown etiology (cryptogenic)

The term idiopathic (genetic) is not used for the etiology of SE.

3. EEG correlates diagnostic axis

When we speak about EEG correlates of SE, it is important to bear in mind the following features:

1. EEG (especially EEG monitoring) is extremely important in case of non-convulsive SE when clinical manifestations are discrete, unspecific and mainly comprise awareness impairments and behavioral alterations
2. Currently, there are no evidence-based EEG criteria for SE.
3. Epileptic discharges are considered distinctive feature, however in case of longer duration of SE, rhythmic non-epileptic patterns may prevail.

The following terminology for description of EEG patterns is proposed:

1. **Localization:** generalized, lateralized, bilaterally independent, multifocal.

2. **Pattern name:** periodic discharges, rhythmic delta activity or spike-wave/ spike-wave plus subtypes.

3. **Morphology:** form, number of phases, amplitude, polarity.

4. **Time-related characteristics:** frequency, duration, onset (gradual, sudden), dynamics (evolving, fluctuating and persisting).

5. **Modulation:** stimuli-provoked or spontaneous.

6. **Effect of drug intervention on EEG finding.**

7. **Fluctuation** - existence or more than 3 changes in frequency (by at least 0,5 Hz), morphology or localization, within a period not longer than 1 minute.

8. **Evolution** - in case of at least 2 firm changes in frequency (at least 2 subsequent one-way changes with at least 0,5 Hz), morphology (at least 2 subsequent changes until the occurrence of new morphology) or localization (subsequent dissemination to at least 2 different standard 10-20 leads).

9. **EEG improvement** upon reducing the pathological finding to rare (up to 1-9% of age).

Modified criteria of Salzburg consensus for non-convulsive SE

In 2013 in Salzburg working EEG criteria for diagnosis of non-convulsive SE were approved. Based on this, in 2015 Leitinger et al. presented the Modified Salzburg Criteria for Non-Convulsive SE, which achieve significant reduction of false positive diagnosis of non-convulsive SE with minimum loss of sensitivity. According to these criteria, the diagnosis of non-convulsive SE is based on a combination of EEG and clinical data, whereas the clinical symptoms suspicious for SE should continue at least 10 minutes. The application of these criteria is recommended for all patients with quantitative or qualitative awareness impairment. They comprise:

Diagnosis-supporting clinical data:

- Exasperated condition within minutes to hours.
- Lack of significant improvement during the last minutes to hours.
- Lack of significant improvement during the last minutes to hours.

Lack of metabolic disorders or data for neuro depicting methods explaining the EEG finding.

EEG alterations with duration of at least 10 sec.:

A. In patients without known encephalopathy (at least 1 criterion of 1 to 3 is necessary 1-3)

1. Epileptic discharges with frequency exceeding 2,5 Hz.
2. Typical ictal evolution in time and space of epileptic discharges or rhythmic activity (exceeding 0,5 Hz).
3. Discrete clinical manifestations (slight flickers in perioral, periorbital area or extremities, close to manifestation with EEG finding in terms of time) with epileptic discharges or rhythmic activity (exceeding 0,5 Hz).
4. In case criteria 1 to 3 are not observed and epileptic discharges with frequency of $\leq 2,5$ Hz exist with fluctuation or rhythmic activity in excess of 0,5 Hz with fluctuation, and after considering the clinical

picture, adequate antiepileptic drugs are applied and the reactivity of the patient is documented after ten minutes.

B. In case of patients with known epileptic encephalopathy

Criteria of group A+ more strongly expressed in terms of level of manifestation or frequency, EEG alterations or clinical and EEG improvement as a result of intravenously applied ASD.

Age diagnostic axis

Modern classification of SE (age)

1. Neonatal period (0-30 days)
2. Infancy (1 month – 2 years)
3. Childhood (2-12 years)
4. Adolescent and adulthood (12-59 years)
5. Elderly (≥ 60 years)

VI. Diagnosis

A patient is diagnosed with epilepsy if at least 2 unprovoked/ provoked epileptic seizures or 1 unprovoked/ provoked seizure and high probability of subsequent seizure exist. This diagnosis is defined in four successive stages (Figure 2):

1. Determination of the seizure – differential diagnosis between epileptic and non-epileptic seizures:
 - Differentiation from non-epileptic paroxysmal conditions such as: syncope, migraine, transitional ischemic attacks, motor disorders, incl. dystonic attacks, oculogyric crises, sleep disorders (parasomnias in REM and non-REM sleep), panic attacks, etc.
 - Making a difference from non-epileptic seizures (pseudo epileptic seizures and syncope with anoxic seizure, panic attacks)
 - Making a difference from seizures in the course of metabolic disorders, traumas, strokes, intoxication with medicines, sudden termination of therapy, alcohol, alcohol abstinence, etc., as well as from febrile seizures in childhood
2. Determination of the type of epileptic seizure (in accordance with the International Classification of Epileptic Seizures) according to clinical characteristics with EEG feature assessment (EEG, video-EEG) and neuroimaging studies (Table 8)

Table 8. Certain auras and their neuroanatomical localization (Wolf P, Dimova P.).

Aura phenomenon	Probable localization of epileptic activity
Affective, <i>e.g.</i> fear, depression, joy Anxiety (sudden, brief, intense, without contents)	Temporal Amygdala
Auditory, <i>e.g.</i> sounds, noises or single tones Music	Heschl's gyrus, if directed lateralizing to opposite side Temporal
Autoscopy, <i>i.e.</i> perceiving a double of oneself	Parietal, probably right
Cephalic, <i>i.e.</i> sensation in the head, <i>e.g.</i> light-headedness	Frontal
Dyscognitive, <i>i.e.</i> disturbance of components of cognition, <i>e.g.</i> impaired understanding, scattered thinking, dream-like states	Temporal
Epigastric, <i>i.e.</i> abdominal sensation that may rise to the chest or throat	Temporal (mesial)
Experiential (recall of certain old memories) Forced thinking	Temporal Frontal, probably left
Gustatory, <i>e.g.</i> bitter, acidic or metallic taste	Temporal
Hallucinatory, <i>i.e.</i> composite perceptions, <i>e.g.</i> “hearing” and/or “seeing” people Hemineglect	Depends on involved perceptions Opposite parietal lobe
Limb pain Mnemonic, <i>i.e.</i> ictal dysmnesia, <i>e.g.</i> <i>déjà-vu</i> (familiarity) or <i>jamais-vu</i> (unfamiliarity)	Opposite postcentral gyrus, parietal operculum Temporal
Olfactory, usually disagreeable odour	Temporal
Somatosensory	Parietal, lateralizing to opposite side
Visual, <i>e.g.</i> flickering lights or amaurosis	Occipital, lateralizing if directed

3. Classification of epileptic syndrome (in accordance with the International Classification of Syndromes)
4. Clarification of the etiology of the disease with neuroimaging, laboratory, metabolic, genetic and other investigations.

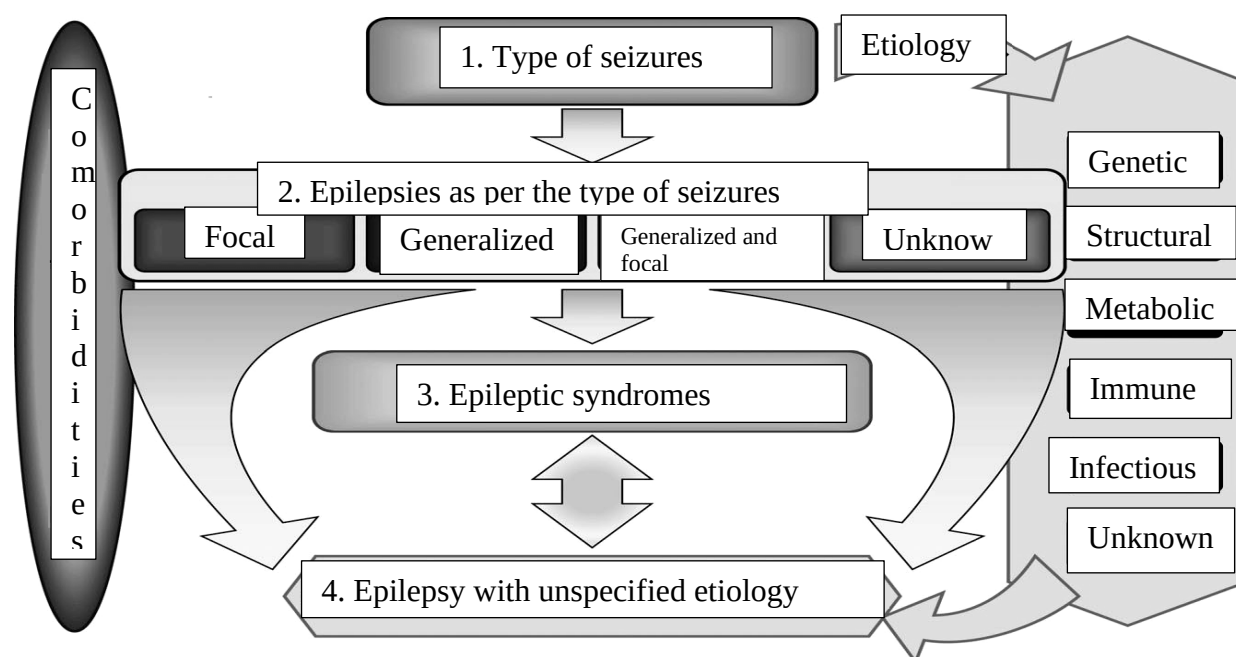


Figure 2. Diagnostic Process in Patients with Epileptic Seizures

The investigations required for diagnosis and follow-up of treatment comprise EEG, neuroimaging investigations and follow-up of ASD serum levels.

- Neurological investigation – on regular basis.
- EEG and regular EEG follow-up, depending on the therapeutic effect, in case of seizures under therapeutic controlled– every 6 months. EEG is required to find the type of epileptic seizures and for proving the photoparoxysmal response (table 7). *EEG during sleep* can be performed in case of indications in children and young people after sleep deprivation or use of melatonin. Video-EEG is required in patients with diagnostic difficulties.

Table 9. Differential Diagnosis of Epileptic Seizures in Accordance with the ILAE International Classification of Epileptic Seizures by Clinical and EEG Indications

Epilepsy – seizures	EEF -ictal	EEG interictal
I. Focal seizures		
Focal seizures – without awareness impairment	Local contralateral discharges with onset in specific area. Not always registered in the scalp	Localized contralateral discharge
Focal seizures – with awareness impairment	Unilateral or more frequently bilateral discharges, diffuse or focal, temporal or frontal-temporal	Unilateral or bilateral, more frequently asynchronous focus, usually T or F

Focal seizures evolving to bilateral tonic-clonic	The discharges described above are quickly generalized secondarily	
II. Generalized seizures		
Absences- impaired awareness	Regular and symmetric 3 Hz, however 2 to 4 Hz spike-wave complexes are possible, sometimes polyspike-wave, bilaterally synchronous appearing against the background of normal EEG.	The main activity is in normal ranges, however the described paroxysmal manifestations of spike-wave complexes 3/s appear, regular and symmetric.
Atypical absences They may be accompanied by alterations in the muscle tonus	Polyfrequent, asymmetric spike-wave complexes or another type of paroxysmal activity occurring against the background of main activity that is abnormal for the age. Alterations are bilateral but are often irregular and asymmetric.	Alterations in the main activity, irregular and asymmetric spike-wave complexes
Myoclonic seizures	Polyspike-wave and spike-wave complexes	The same as the ictal activity
Tonic seizures	Quick activity, or 9-10/s rhythm or with decreasing frequency and increasing amplitude	Rhythmic discharges of spikes and waves, sometimes asymmetric, often abnormal main activity
Clonic seizures	Quick activity (10 s and more) and slow waves, rarely spike-wave complexes	Spike-wave or polyspike-wave discharges
Tonic-clonic seizures	Rhythm of 10 or more seconds with decreasing frequency and increasing amplitude during the tonic phase, with interruptions of slow waves during the clonic phase	Polyspike-wave or spike-wave, or sharp-slow complexes
Atonic seizures	Polyspike-wave complexes, more rarely low voltage quick activity	Polyspike-wave complexes

- The lack of EEG abnormalities does not exclude the epilepsy diagnosis.
- The lack of epileptiform activity in EEG in the course of the conducted antiepileptic treatment does not mean that the treatment is possibly effective.

➤ The epilepsy may not be diagnosed only on the grounds of EEG epileptiform activity without the respective clinical manifestation.

- **Neuroimaging investigations**

- ***Urgent:***

- Patients suffering epileptic seizures for the first time, with newly occurred focal neurological deficiency, awareness impairment (with or without data for intoxication), fever, head trauma, persisting headache, medical history of neoplasm or administration of anticoagulants, HIV positive result, existence of focal seizures in patients at the age of 40+.

- Patients with known epilepsy in case of: suspected cerebral-structural lesions based on progressive neurological deficiency; awareness impairment (with or without intoxication), fever, cranial trauma, persisting headache, medical history of neoplasm or administration of anticoagulants, change of the type of seizures, progressive intellectual deficiency.

- **Computer tomography (CT) of cerebrum** is indicated in case of emergency, as well as for visualization of cerebral calcifications (tuberous sclerosis, etc.) CT with contrast – for differentiation of arteriovenous malformation, cerebral tumor. Repeated CT investigations – in case of progressive changes of the neurological status and therapeutic resistance.

- **Magnetic-resonance imaging (MRI) of cerebrum** is a method to be chosen by the patients suffering epilepsy due to the opportunity to visualize small-size lesions (cortical dysplasia and deficiency of neural migration), hippocampal sclerosis and neoplasms. It is indicated in case of patients with focal epilepsy, except for proved idiopathic childhood focal epilepsies, as well as for newly occurred epilepsy after the age of 25 for clarification of symptomatic etiology. Repeated MRI investigations – in case of therapeutic resistance of epilepsy and/or progressive changes of the neurological status.

- **Transfontanellar ultrasound** – during infancy.

- **CBC (complete blood count), transaminases, electrolytes** – at the beginning of treatment as well as other indicators, if necessary. In case of normal values – follow-up investigations every 6 months.

- **ECG** of children and adults in case of suspicions for epilepsy and DD with syncope or rhythm disorders.

- **Eye status**

- **Investigations of ASD level** – after the end of titration of valproates, carbamazepine, phenytoin, followed by once a year monitoring. In case of suspicions for low level or intoxication, therapeutic resistance, more than 2 drugs, liver and kidney failure, forensic medical expertise. In case of pregnant women – monthly follow-up of serum levels.

- **Psychological investigation** in case of learning difficulties and regular follow-up for assessment of possible regress of cognitive functions.

- **Genetic investigations** (Tables 1, 2, 3, 4)

In case of partial (focal) epilepsies, existence of SGTCS and some unspecified syndromes the following additional investigations should be performed:

- Doppler and transcranial Doppler sonography.
- MR angiography in case of suspicions for arteriovenous malformation (AMV), stenosis and hypoplasia of interior carotid, middle cerebral artery.
- Cerebral angiography – in case of suspicions for cerebrovascular malformations after CT, CT with contrast, MR angiography.
- Functional neuroimaging examinations – SPECT and PET for finding local hypo-/ hyperfusion and hypo- or hypermetabolism.
- **Cerebrospinal fluid examination** – in case of suspicions for meningitis, acute or subacute encephalitis, subarachnoid hemorrhage, leukodystrophy

VII. Therapy

Timely diagnostics of the type of seizures and epileptic syndrome is a condition precedent for the appropriate choice of antiepileptic therapy determining to the greatest extent the forecast and psychological and socioeconomic issues related to epilepsy. Treatment of patients with epilepsy is carried out by specialists-neurologists and/or child neurologists. Consultation with psychiatrist is necessary in case of psychosis, change of personality, epilepsy-related psycho-social dysfunction.

The aims of the antiepileptic treatment are full control of epileptic seizures or reduction of seizure frequency and/or gravity, better endurance, safety, and taking into account medicine interactions, suppression of subclinical epileptic activity and of epileptogenesis, improvement of the quality of life.

Epilepsy therapy includes drug therapy (monotherapy, rational polytherapy) and if needed (medication resistance or some specific syndromes) – neurosurgical treatment, alternative therapies (ketogenic diet and modifications, vagus nerve stimulation). The choice of anti-seizure drug (ASD), the duration of therapy and the decision for hospitalization are made by specialist neurologists and/or child neurologists. Some main principles are observed with regard to the epilepsy treatment.

In case of a **single tonic-clonic epileptic seizure** treatment is started in case of high risk of recurrences: EEG with interictal epileptiform abnormalities and/or persisting cause for epileptic seizures like cortical dysplasia seed in MRI; initial unprovoked status epilepticus; medical history of previous myoclonia, absences. The main purpose of the therapy is full control of seizures with minimum adverse effect of ASD, by achieving the best possible quality of life. The benefit and risks of continuous administration of ASD on case by case basis should be assessed.

The antiepileptic drug therapy starts in case of ***firm diagnosis***: according to the new definition, after 2 unprovoked or provoked seizures occurring within a period longer than 24 hours, after 1

unprovoked (or provoked) seizure at least 30 days after neuroinfection, stroke, cerebral trauma, or after diagnosing an epileptic syndrome. In case of idiopathic childhood focal epilepsy with central temporal spikes (Rolandic), some forms of photosensitive epilepsies, febrile seizures or rare epileptic seizures (seizures rarer than once a year or rare and slight nocturnal seizures) and in case of short-lasting focal seizures treatment is not always necessary.

A. Principles of Treatment

1. The type of epilepsy, the type of seizures, indications and risk factors for anti-convulsive therapy are assessed
2. The treatment begins with monotherapy with ASD *first line drug* according to the type of seizures, the epileptic syndrome, the age of the patient, the existence of comorbidities, co-medications. The advantages of monotherapy comprise low toxicity, good tolerability, lack of medication interaction, minimized cognitive disorders and other adverse reactions. The effect is controlled in accordance with the clinical symptoms (frequency and gravity of seizures) and by means of EEG.
3. The treatment starts with low dose, which is gradually increased up to seizure or side reaction control.
4. Monitoring of serum levels.
5. Assessment of the risk of reoccurrence of seizures upon termination or change of treatment.
6. Achievement of optimal quality of life.
7. In case of therapeutic-resistant epilepsies (failure of two adequate AMD) – referral to specialized clinics for investigations aimed at etiological clarification, determination and conducting of rational polytherapy and discussion for possible neurosurgical treatment and ketogenic diet.

B. Anti-Seizure Drugs

Modern treatment of epilepsy in children and adults is carried out with the following ASD in accordance with the registered indications, such as monotherapy or rational polytherapy, adequate for the type of epilepsy and the type of seizures, depending on the patient's age, weight and somatic comorbidities (liver, kidney, blood, etc.) and the risk of teratogenicity in young women with generative potential: Carbamazepine (CBZ), Cannabidiol* (CBD), Clobazam**, Clonazepam (CZP), Eslicarbazepine (ESL), Ethosuximide (ESM), Fenfluramine* (FFL), Gabapentin (GBP), Lacosamide (LCM), Lamotrigine (LTG), Levetiracetam (LEV), Nitrazepam**, Oxcarbazepine (OxCBZ), Phenobarbital (PB), Phenytoin (PHT), Pregabalin (PGB), Retigabine (RGB), Rufinamide*, Stiripentol*, Sulthiam**, Tiagabine (TGB), Topiramate (TPM), Valproate (VPA) Vigabatrin**, Zonizamide**, Methylprednisolon, Piracetam (PZT), Brivaracetam (BRV) (Tables 10, 11, 12, 13, 14 and 15).

* Registered in Bulgaria in accordance with the centralized procedure

****Not registered in Bulgaria**

The possibility of suicidal behavior or ideation due to AED should be considered.

C. Initial Treatment of Epilepsy.

The treatment starts with monotherapy with ASD first choice drug, depending on the type of epilepsy and the type of seizures after two unprovoked seizures (Table 10), by achieving optimal dose (Table 11). Monotherapy is efficient in 60% of newly diagnosed patients (I monotherapy – 47%, or II monotherapy – in 13%).

I monotherapy (first choice drug) comprises:

- **Valproate** - for generalized, focal epilepsies or in case of suspicions in the classification of seizures, in case of West syndrome. Teratogenic effect of VPA is possible in young women with generative potential and in pregnant women.
- **Carbamazepine** - for focal epilepsies or **Oxcarbazepine** – in childhood. The retard forms of Carbamazepine are recommended.
- **Ethosuximide**, and if indications exist **Lamotrigine** too, are first choice drugs in case of absences.
- Broad-spectrum ASD, such as **Valproate, Lamotrigine, Levetiracetam, Topiramate**, Broad-spectrum ASD, such as are first choice drugs in patients with more than one type of seizures (especially if absences, atonic and myoclonic seizures occur).
- **Some of the new ASD (Lamotrigine, Oxcarbazepine)** may be applied as monotherapy in case of *special conditions* (childhood – adolescence, young women and pregnant women, cognitive deficiency), side reactions or organ failure.

II monotherapy (alternative monotherapy) is applied in case of treatment effect, intolerance, side reactions or organ failure, by adding another appropriate ASD and gradually removing the first one:

- in case of generalized and focal seizures with or without secondary generalization, polymorphic seizures, Lennox-Gastaut syndrome: LTG, LEV, TPM.
- in case of focal and secondarily generalized seizures: OxCBZ and LCM (above 4 years), ESL (above years).
- in case of West syndrome - CZP, LTG, TPM.

- ASD may possibly cause **deterioration** of some epileptic seizures and syndromes (table 12). In case of treatment of absences and myoclonic seizures in children and adults, carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin are not recommended, and in case of Dravet syndrome – high doses of lamotrigine too, due to risk of aggravation. Lamotrigine may exasperate the condition of patients with juvenile myoclonic epilepsy. In children with self-limited epilepsies (idiopathic focal epilepsies Rolandic type, Panayotopoulos syndrome, and Gastaut type),

carbamazepine and oxcarbazepine may exasperate the condition of patients up to the manifestation of CSWS.

• **Reasons for the failure of monotherapy are:**

1. Inappropriate diagnosis (cerebral tumor, pseudo epileptic seizures, syncope, heart arrhythmia, etc.)
2. Inappropriate choice of ASD (inappropriate for the type of seizures, medication interactions)
3. Inappropriate dose, side reactions
4. Inappropriate lifestyle (alcoholism, drug dependence, etc.)

Table 10. Anti-Seizure Drugs for Treatment of Epilepsies (Syndromes) and Epileptic Seizures

Type of epilepsy (syndrome) epileptic seizures	1 st choice monotherapy	Alternative monotherapy or polytherapy
Primarily generalized (idiopathic/ genetic) epilepsies/ generalized seizures		
Tonic-clonic seizures	CBZ,PHT,VPA	CZP, LTG, LEV, OxCBZ, PB, TGB, TPM,
Atonic seizures	VPA	LTG, CZP
Absences	VPA, ESM	CZP, LTG, TPM
Myoclonic seizures	VPA	CZP, ESM, LTG, LEV, TPM, Corticosteroids
Juvenile myoclonic epilepsy	VPA	CZP, ESM, LTG, LEV, TPM
Focal epilepsies/ focal epileptic seizures		
Focal seizures	CBZ, VPA	CZP, GBP, LCM, LTG, LEV, OxCBZ, PB, PHT, PGB, TGB, TPM, BRV, ESL
Secondarily generalized seizures	CBZ, PHT, VPA	GBP, LTG, LCM, LEV, OxCBZ, PB, PHT, PGB, TGB, TPM, BRV, ESL
Idiopathic focal (Rolandic and occipital)	CBZ, VPA, OxCBZ	CZP, GBP, LTG, LEV
Epilepsies encephalopathies / developmental encephalopathies		
West syndrome	ACTH, VPA	CZP, LTG, TPM, VGB**, ZNS**
Lennox-Gastaut syndrome	LTG, TPM, VPA	CBZ, CZP, PB, PHT, Rufinamide*, Cannabidiol* with Clobazam**, ZNS**, Fenfluramine*
Dravet syndrome (SMEI)	VPA,TPM	LEV, Stiripentol*, Cannabidiol* with Clobazam**, Fenfluramine*

Epileptic encephalopathy with CSWS or electric stratus during slow-wave sleep (ESES)	VPA, ESM	LEV, benzodiazepines, corticosteroids
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- **ASD allowed as monotherapy and supplementary therapy: CBZ, CZP, ESM, GBP** (above 12 years – mono-, above 3 years - polytherapy), **ESL** (above 18 years mono-, above 6 years polytherapy) **LTG** (above 2 years), **LEV** (above 16 years – monotherapy, more than 1 month – polytherapy), **LCM** (above 4 years), **OxCBZ, PHT, PB, TPM** (above 2 years), **VPA**

- **ASD allowed only as supplementary therapy: PGB** (above 18 years); **TGB** (above 12 years), where other appropriate drug combinations have proved to be unsatisfactory or are intolerable, **BRV** (above 4 years)

- **Classical ASD: CBZ** - carbamazepine; **CZP**-clonazepam; **ESM**– ethosuximide, **PHT**- phenytoin; **PB**-phenobarbital; **VPA**-valproate

- **New ASD: GBP**-gabapentin; **ESL**- eslicarbazepine; **LTG** - lamotrigine; **LCM** – lacosamide; **LEV**- levetiracetam; **OxCBZ** - oxcarbazepine; **PGB** – pregabalin; **TGB**-tiagabine; **TPM** – topiramate; **Rufinamide***- for Lennox-Gastaut syndrome; **Stiripentol***- for Dravet syndrome; **BRV** – brivaracetam (above 2 years), **CBD - Cannabidiol*** in epileptic seizures associated with tuberous sclerosis complex (TSC) in patients ≥ 2 years; **CBD - Cannabidiol*** in combination with Clobazam** in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years; **FFL - Fenfluramine***- for Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years, **Cenobamate****- for adjunctive treatment of focal-onset seizures with or without secondary generalisation over 18 years; **Zonisamide**** for treatment of focal and secondarily generalized seizures in adults and children at the age of 6+, for myoclonic seizures, for Lennox-Gastaut syndrome;

***In the list under article 266, paragraph 2 of the Medicinal Products in Human Medicine Act and article 16, paragraph 4 of Ordinance No 10 of 2011 on the terms and conditions for treatment with medicinal products not allowed for use in the Republic of Bulgaria:**

* **Rufinamide** for treatment of Lennox-Gastaut syndrome

* **Stiripentol** for treatment of Dravet syndrome

* **Cannabidiol** in combination with Clobazam** in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years; * **Cannabidiol** in the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients ≥ 2 years of age

***Fenfluramine** - in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years

**** Registered by EMA:**

Clobazam** for treatment of absences, GTCS, myoclonus, Dravet syndrome and Lennox- Gastaut syndrome; **Nitrazepam**** for treatment of West syndrome; **Sulthiam**** for treatment of focal seizures; **Vigabatrin**** for treatment of West syndrome; **Zonisamide**** for the treatment of focal and secondary

generalized seizures in adults and children over 6 years of age, for myoclonic seizures, for Lennox-Gastaut syndrome; **Cenobamate****- for adjunctive treatment of focal-onset seizures with or without secondary generalisation over 18 years, **ACTH**** for treatment of West syndrome.

Table 11. Types and Dosage of Anti-Seizure Drugs

International nonproprietary name (INN)	CHILDREN		ADULTS		
	Initial daily dose (mg/kg)	Optimal daily dose (mg/kg)	National daily dose (mg)	Optimal daily dose (mg)	Maximum daily dose (mg)
Valproic acid	10-20	10-50	500	1000-2000	2100
Carbamazepine	5	10-30	200	600-1200	1600
Oxcarbazepine	10	30-40	300-600	900-2400	2400
Phenytoin	3-4	4-8	100	300-400	500
Phenobarbital	2	2-5	60	90-250	600
Clonazepam	0,01	0,01-0,02– 0,1-0,2	0,5	2-6	8
Lamotrigine	0,6 with enzyme inductors 0,15 in case of VPA 0,3 during monotherapy	5-15 with enzyme inductors 5 with VPA 15 during monotherapy	50 with enzyme inductors 12,5 with VPA 25 during monotherap y	500-600 with enzyme inductor 300-400 with VPA 500 during monotherapy	700 during monotherapy
Topiramate	0,5-1,0	5-9	25	200-400	500
Levetiracetam	10	40	1000	2000-3000	3000
Tiagabine	0,1	1	5–10	60	70
Gabapentin	After 6 years 10-15	30-35	300	1200-1800- 3600	3600
Pregabalin	-	-	150	450-600	600
Lacosamide	After 4 years 2 mg/ kg	200-400 mg/day	100	200-400	600 mg or 10 mg/kg during monotherapy of children and adolescents above 50 kg and 8 mg/

					kg in children and adolescents under 50 kg; 400 mg in case of supplementary therapy for children and adolescents above 50 kg and adults
Ethosuximide	10	40	500	1500	2000
Stiripentol*	50	до 100	50	до 100	4000
Rufinamide*	Above 4 years - 10	45	400	2400	3200
Brivaracetam	-Above ≥ 4 years and adolescent ≥ 50 kg - 1 mg/kg -Above 16 years 50 - 100, divided in two equal doses	- Above ≥ 4 years and adolescent ≥ 50 kg - 2 mg/kg - 50-200 based on the individual response and tolerability	50 - 100, divided in two equal doses	50-200 based on the individual response and tolerability	200
Eslicarbazepine	- Above 6 years -10 mg/kg/daily - Above 60 kg - 400 mg	Above 6 years - 30 mg/kg	400 mg once daily	800-1200 maximum 1600 mg once daily	1600
Clobazam**	Above 2 years -0,4-1 mg/kg	Titrate to 1 mg/kg every 7 days; Under 30 kg - 20 mg; Above 30 kg - up to 40 mg	5 mg	Up to 40 mg	40 mg
Zonisamide**	≥ 6 r. and adolescent ≥ 50 kg- 1 mg/kg	Titrate over 7 days to 4-8 mg/kg	100 mg	300 mg	600 mg

Cannabidiol*	≥ 2 years -2.5 mg/kg twice (5 mg/kg/day), titrate over 7 days to 10-20 mg/kg	For LGS and Dravet syndrome - up to 10 mg/kg/day; For TSC-10 mg/kg/day			For LGS and Dravet syndrome - 20 mg/kg/day For TSC – 25 mg/kg/day
Fenfluramine*	≥ 2 years - 0.2 mg/kg/day - up to 0.7mg/kg/day maximum up to 26 mg/day	For Dravet syndrome up to 0.4 mg/kg/day with Stiripentol up to 0.7 mg/kg/day without Stiripentol; For LGS - 0.2 mg/kg/day - up to 0.7 mg/kg/day	0,4 mg/kg/day	0.7mg/kg/day For DS up to 17mg/day with Stiripentol, up to 26mg/day without Stiripentol, For LGS up to 26 mg/day	26 mg/day
Cenobamate**	-	-	12.5 mg once	Titrate in 14 days - 25 mg, 50 mg, 100 mg, 150 mg to 200 mg	400 mg

***In the list under article 266, paragraph 2 of the Medicinal Products in Human Medicine Act and article 16, paragraph 4 of Ordinance No 10 of 2011 on the terms and conditions for treatment with medicinal products not allowed for use in the Republic of Bulgaria:**

- * **Rufinamide** for treatment of Lennox-Gastaut syndrome
- * **Stiripentol** for treatment of Dravet syndrome
- * **Cannabidiol** in combination with Clobazam** in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years; * **Cannabidiol** in the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients ≥ 2 years of age
- ***Fenfluramine** - in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years

**** Registered by EMA:**

Clobazam** for treatment of absences, GTCS, myoclonus, Dravet syndrome and Lennox- Gastaut syndrome; **Nitrazepam**** for treatment of West syndrome; **Sulthiam**** for treatment of focal seizures; **Vigabatrin**** for treatment of West syndrome; **Zonisamide**** for the treatment of focal and secondary generalized seizures in adults and children over 6 years of age, for myoclonic seizures, for Lennox-

Gastaut syndrome; **Cenobamate****- for adjunctive treatment of focal-onset seizures with or without secondary generalisation over 18 years, **ACTH**** for treatment of West syndrome.

Table 12. Possible deterioration of epileptic syndromes due to ASD

ASD	Syndrome	Possible worsening
Carbamazepine	• Absence epilepsy • Juvenile myoclonic epilepsy • Progressive myoclonic epilepsy • Rolandic epilepsy • Childhood occipital epilepsy • Symptomatic generalized epilepsies • Angelman syndrome • Landau-Kleffner syndrome	• Absences, myoclonia • Myoclonic seizures • Myoclonus • CSWS • GTCS – rarely • Focal seizures – rarely • Tonic seizures • Atonic seizures
Oxcarbazepine	• Absence epilepsy • Juvenile myoclonic epilepsy • Rolandic epilepsy	• Absences • Myoclonia • Focal seizures
Phenytoin	• Absence epilepsy • Progressive myoclonic epilepsy • Juvenile myoclonic epilepsy • Landau-Kleffner syndrome	• Absences • Cerebellar syndrome • Myoclonic seizures • Focal seizures – rarely • GTCS
Phenobarbital	• Absence epilepsy • Rolandic epilepsy • Lennox-Gastaut syndrome	• Absences (in case of high doses) • Myoclonic seizures
Valproate	• Absence epilepsy • Single cases in case of epilepsy with myoclonus and cryptogenic focal epilepsy	• Absences • Myoclonic seizures • Focal • GTCS
Ethosuximide	• Absence epilepsy • Epilepsy with myoclonus • Epilepsy with GTCS	• Absences • Myoclonic seizures • GTCS
Benzodiazepines	• Lennox-Gastaut syndrome	• Tonic seizures • Absences • Myoclonic seizures
Vigabatrin	• Absence epilepsy	• Absences

	• Epilepsies with myoclonus • Lennox-Gastaut syndrome	• Myoclonus • Focal seizures • Tonic seizures
Gabapentin	• Absence epilepsy • Epilepsy with myoclonus • Lennox-Gastaut syndrome	• Absences • Myoclonus
Lamotrigine	• Early severe myoclonic epilepsy • Juvenile myoclonic epilepsy • Rolandic epilepsy	• In case of high doses • Myoclonic seizures
Rufinamide	• Lennox-Gastaut syndrome	• Atonic seizures
Topiramate	• Absence epilepsy	• Absences
Tiagabine	• Absence epilepsy • Epilepsy with myoclonus	• Absences • Myoclonic seizures • Focal • GTCS
Levetiracetam	• Juvenile myoclonic epilepsy • Absence epilepsy • Lennox-Gastaut syndrome • Dravet syndrome	• Absences • Myoclonic seizures • Focal • GTCS
Pregabalin	• Absence epilepsy • Epilepsy with myoclonus	• Absences • Myoclonic seizures
Lacosamide	• Lennox-Gastaut syndrome	• Atypical absences • GTCS

D. Treatment with Polytherapy – the treatment starts in case of patients *without effect of monotherapy with 2 ASD*. It is applied in about 40% of patients for whom monotherapy is ineffective: frequent, severe focal or polymorphic seizures, specific syndromes and epileptic encephalopathies, for example temporal lobe epilepsy in case of mesial temporal sclerosis, severe childhood myoclonic epilepsies (SMEI), West syndrome, Lennox-Gastaut syndrome. Upon adding a second, respectively, third ASD, rational polytherapy is recommended by combining 2 (3) ASD with different action mechanism (Table 11).

Some ASD (lamotrigine, topiramate, valproic acid) have plenty of mechanisms of action, and other (phenytoin, carbamazepine, ethosuximide) – one single mechanism of action. ASD are classified in the following groups according to their mechanism of action:

1. Blockers of repetitive activation of sodium channels - phenytoin, carbamazepine, oxcarbazepine, lamotrigine, topiramate, rufinamide
2. Increasing the slow inactivation of sodium channels - lacosamide
3. Increasing the GABA-A receptors - phenobarbital, benzodiazepines
4. Modulators of Glutamate - topiramate, lamotrigine
5. Blockers of T- calcium channels - ethosuximide, valproate
6. Blockers of N- и L- calcium channels - lamotrigine, topiramate, valproate
7. Modulators of H-flows - gabapentin, lamotrigine
8. Blockers of unusual sites – levetiracetam, brivaracetam (high and selective affinity to protein 2A (SV2A) of synaptic vesicles in the brain, which modulates the exocytosis of neurotransmitters) fenfluramine - affects serotonin (5-HT) metabolism, $\sigma 1$ (sigma-1) receptors; cannabidiol -through TRPV1, GPR55 and ENT-1 receptors
9. Carbonic anhydrase inhibitors - topiramate

Table 13. Main Mechanisms of Action of ASD

ASD	Blockin g/ modulat ion of Na ⁺ channel s	Blocking/ modulation of Ca ²⁺ channels	GABA increase	Blocking of glutamate receptors	Antoher
Phenytoin	+	-	-	-	
Carbamazepine	+	-	-	-	
Phenobarbital	+	-	+	-	
Primidone	+	-	+	-	
Valproate	+	+ (T-type)	+	-	
Ethosuximide	-	++ (T- type)	-	-	
Clonazepam	-	-	+	-	
Gabapentin	+	+ (L- type)	-	-	
Lamotrigine	+	+ (L- type)	-	-	
Oxcarbazepine	+	-	-	-	
Eslicarbazepine	+				
Topiramate	+	+ (L- type)	+	+ (AMPA)	Inhibits

					carbonic anhydrase
Tiagabine	-	-	+	+(NMDA)	
Levetiracetam					Blocker of SV protein
Pregabalin		+	+		
Lacosamide	+				
Brivaracetam					Blocker of SV2A protein, modulates the exocytosis of neurotransmitters
Clobazam			+		
Cannabidiol					TRPV1,GPR55, ENT-1
Fenfluramine					serotonin (5-HT) metabolism; σ 1 (sigma-1) receptors
Cenobamate	+				
Zonisamide	+	+ (T type)	+	+	

GABA= gamma aminobutyric acid

AMPA=aminomethylisoxazole propionate

NMDA=N-methyl-D-aspartat

SV2A – synaptic vesicle protein 2A

Some appropriate combinations are recommended in case of resistant seizures (Table 12).

According to the registered indications the supplementary therapy includes the following new ASD:

- In case of **generalized and focal seizures: LTG, LEV, TPM**
- In case of **focal and secondarily generalized seizures: GBP** (above 6 years), OxCBZ, **PGB** (above 18 years), **LCM** (above 4 years); BRV (above 4 years); ESL (above 6 years); **TGB** above 12 years, where other appropriate drug combinations have proved to be unsatisfactory or intolerable. **Cenobamate** - for adjunctive treatment of focal-onset seizures with or without secondary generalisation over 18 years; **Cannabidiol**** in combination with Clobazam** for relapses associated with tuberous sclerosis complex (TSC) in patients ≥ 2 years.
- In case of **Lennox-Gastaut syndrome** - LTG, TPM, Rufinamide*, **Cannabidiol** * in combination with Clobazam** ≥ 2 years, **Fenfluramine*** ≥ 2 years.
- In case of **Dravet syndrome (SMEI)** - LEV, TPM, Stiripentol*, **Cannabidiol** * in combination with Clobazam** ≥ 2 years, **Fenfluramine*** ≥ 2 years.

Table 14. Recommended Combinations of AED for Drug Resistant Seizures

Combinations	Appropriate	Causes
PHT or CBZ+		
LTG	-	Neurotoxic side reactions
OXC	-	Neurotoxic side reactions
ESL		Neurotoxic side reactions
TPM	-	Neurotoxic side reactions
LEV	+	Synergism
BRV	+	Synergism?
LTG or OXC+		
Gabapentin	++	Synergism
Pregabalin	++	Synergism
LEV	++	Synergism
BRV	++	Synergism?
TPM	+	Synergism
VPA +		
PHT	-	
CBZ	-	
LTG	±	Risk of rashes
TPM	±	Neurotoxic side reactions
LEV	++	Synergism
BRV	++	Synergism?
LCM	+	Synergism

* Clonazepam may be added to all ASD

E. Specificities of the application of ASD in case of different types of epilepsy in children, pregnant women, elderly patients and patients with intellectual deficiency, with depression, with liver or kidney failure

Epilepsy in childhood. The choice of ASD for different types of epilepsies and syndromes in childhood is presented in table 15, and the initial and optimal doses – in tables 11 and 16.

Table 15. Choice of ASD in Childhood for Epilepsies/ Epileptic Syndromes – I, II Monotherapy, Supplementary Therapy

Epilepsy/ syndrome	I monotherapy	Alternative mono- / supplementary therapy	Possible mono-/ supplementary therapy
West syndrome	ACTH	VPA	Benzodiazepines, TPM
Dravet syndrome (SMEI)	VPA, TPM	Benzodiazepines, VPA	LEV, Stiripentol**, CBD* in combination with Clobazam** $\geq$ 2 years, Fenfluramine * $\geq$ 2 years, ZNS** $\geq$ 6 years.
Lennox-Gastaut syndrome	VPA, VPA + LTG	LTG, TPM	Benzodiazepines, CBZ, GBP, LEV, Rufinamide** above 4 years, CBD* in combination with Clobazam** $\geq$ 2years, Fenfluramine * $\geq$ 2 years, ZNS** $\geq$ 6 years.
Epileptic encephalopathy with CSWS or Electric status during slow-wave sleep (ESES)	VPA, ESM	Benzodiazepines, corticosteroids	LEV
IGE with absences	VPA	LTG, ESM	Benzodiazepines
IGE with myoclonus, with or without GTCS	VPA	LTG, ESM	Benzodiazepines, LEV, PB TPM
IGE with myoclonus and GTCS	VPA	LTG, TPM	Benzodiazepines, LEV, PB
IGE with GTCS	VPA	LTG, TPM	LEV, PB, Benzodiazepines,
Focal	CBZ, OxCBZ, VPA	LTG, TPM, GBP	LEV, PB, LCM-above 4 years, BRV above 4 years, ESL above 6 years
Unclassifiable	VPA	TPM	LTG, LEV
Neonatal seizures	PB		

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*** Rufinamide** for treatment of Lennox-Gastaut syndrome

* **Stiripentol** for treatment of Dravet syndrome

* **Cannabidiol** in combination with Clobazam** in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years; * **Cannabidiol** in the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients ≥ 2 years of age

***Fenfluramine** - in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years

**** Registered by EMA:**

Clobazam** for treatment of absences, GTCS, myoclonus, Dravet syndrome and Lennox- Gastaut syndrome; **Nitrazepam**** for treatment of West syndrome; **Sulthiam**** for treatment of focal seizures; **Vigabatrin**** for treatment of West syndrome; **Zonisamide**** for the treatment of focal and secondary generalized seizures in adults and children over 6 years of age, for myoclonic seizures, for Lennox-Gastaut syndrome; **Cenobamate****- for adjunctive treatment of focal-onset seizures with or without secondary generalisation over 18 years, **ACTH**** for treatment of West syndrome.

Table 16. Types of registered ASD for monotherapy and supplementary therapy with indications, incl. for childhood

ASD	Monotherapy	Supplementary
Valproate (10-50 mg/kg)	Absences, GTCS, focal, SGTCS	Absences, GTCS, focal, SGTCS (FBCTS)
Carbamazepin (10-20 mg/kg)	focal, SGTCS	GTCS, focal, SGTCS (FBCTS)
Ethosuximide (15-30 mg/kg)	Absences	
Phenytoin (3-8 mg/kg)	GTCS, focal, SGTCS	GTCS, focal, SGTCS (FBCTS)
Lamotrigine (3-10 mg/kg)	Absences - initial therapy; 2-12 years – monotherapy for IGE, focal seizures, LGS	Above 2 years - supplementary therapy for IGE, focal seizures, Lennox-Gastaut syndrome
Topiramate (3-9 mg/kg)	Above 2 years - generalized and focal epilepsy	Above 2 years - generalized and focal epilepsy, Lennox-Gastaut syndrome
Levetiracetam (40-60 mg/kg)	Above 16 years - initial focal seizures	Over 1 month - focal and SGTCS (FBCTS); over 12 years-myoclonic seizures in juvenile myoclonic epilepsy and GTCS
Oxcarbazepine (30-46 mg/kg)	Above 6 years focal and SGTCS	Above 6 years - supplementary therapy for focal seizures and SGTCS (FBCTS)

Brivaracetam (1-4 mg/kg)	-	Above 2 years - supplementary therapy for focal and SGTCS (FBCTS)
Gabapentin (40 mg/kg)	Above 12 years - focal seizures	Above 6 years - supplementary therapy for focal seizures
Lacosamide (8-10 mg/kg)	At and over 4 years old - monotherapy for focal seizures	Above 4 years - supplementary therapy for focal seizures
Tiagabine (0,1- 1 mg/kg)	-	Above 12 years - supplementary therapy for focal seizures
Eslicarbazepine (10-30 mg/kg)	Above 18 years - focal and SGTCS	Above 6 years - supplementary therapy for focal and SGTCS (FBCTS)
Vigabatrin** from 4 mg/kg titration to 100-150 mg/kg	West syndrome	West syndrome
Rufinamide* - 45 mg/kg	-	Lennox-Gastaut syndrome ≥ 4 years, possibly in epileptic spasms, myoclonic-astatic epilepsy
Stiripentol* - 50- 100 mg/kg	-	Dravet syndrome (SMEI) ≥ 3 years, Resistant focal seizures, status epilepticus
Sulthiam** from 3 mg/kg, titration to 5 - 10 mg/kg	-	Rolandic epilepsy after failure of other ASD; focal seizures and SGTCS (FBCTS), Rett syndrome, epileptic encephalopathies
Clobazam** 0,4-1 mg/kg	-	Lennox-Gastaut syndrome ≥ 2 years, Dravet syndrome ≥ 2 years; Focal and generalized seizures with therapeutic resistance
Zonisamide** ≥ 6 r. and adolescents ≥ 50 kg- 1 mg/kg titration to 8-12 mg/kg	-	Focal and SGTCS ≥ 6 years IGE with GTCS, JME; West Syndrome, Lennox-Gastaut Syndrome, myoclonic-astatic epilepsy
Cannabidiol* 5 mg/kg/day, titration to 10-20 mg/kg	-	Lennox-Gastaut syndrome and Dravet syndrome, in combination with clobazam for patients ≥ 2 years. Treatment of seizures associated with tuberous sclerosis complex (TSC)

Fenfluramine* - ≥ 2 г.- 0,2 mg/kg- до 0,7 mg/kg maximum to 26 mg/day	-	Dravet Syndrome, Lennox-Gastaut Syndrome
Felbamate from 15 mg/kg titration to 30-60 mg/kg up to 12 years	-	West Syndrome, Lennox-Gastaut Syndrome, Landau-Kleffner, JME, but in case of failure of other ASD due to serious adverse drug reactions (liver damage, aplastic anemia, etc.)

***In the list under article 266, paragraph 2 of the Medicinal Products in Human Medicine Act and article 16, paragraph 4 of Ordinance No 10 of 2011 on the terms and conditions for treatment with medicinal products not allowed for use in the Republic of Bulgaria:**

- * **Rufinamide** for treatment of Lennox-Gastaut syndrome
- * **Stiripentol** for treatment of Dravet syndrome
- * **Cannabidiol** in combination with Clobazam** in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years; * **Cannabidiol** in the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients ≥ 2 years of age
- ***Fenfluramine** - in Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years

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Treatment of Febrile Seizures (FS)

1. Acute treatment in case of febrile seizures comprises treatment of the main disease and the continuous FS as well as in status epilepticus with Diazepam - 0,3-0,5 mg/kg, rectally or intravenously. The antipyretic treatment with Paracetamol (Acetaminophen) and Ibuprofen does not change the risk of recurring FG but improves the general condition of the child upon temperature decrease.

2. Prophylactic treatment. Intermittent prophylaxis with Diazepam or constant treatment with Valproate is recommended according to the risk of recurring FS. No treatment is required in case of simple FS. Intermittent prophylaxis of FG with Diazepam decreases the risk of recurring FS. Constant treatment with anticonvulsants in case of FS does not ensure prophylaxis of the risk of epilepsy.

- **Intermittent prophylaxis with rectal or oral Diazepam** is recommended in case of FS with onset under 1 year of age; family history of FS in one of the parents; 2 or more FS or frequent FS (2 for 12 hours, 3 for 6 months or 4 for 1 year): Diazepam - 0,3-0,5 mg/kg rectally in case of t° exceeding

37,5° C every 12 hours (therapeutic plasma concentration after 2-4 minutes) or oral Diazepam - 0,3 mg/kg every 8 hours (therapeutic plasma concentration after 30-90 minutes) to afebrile 24 hours (administration for up to 3 days).

- **In case of high risk of recurring FG** (combination of complicated prolonged FS > 15 minutes, neurological deficiency, under 1 year of age, frequent FS, FS in the first hour of the febrile disease or in case of $t^o < 38^0$) constant prophylactic treatment with Valproate 30 mg/kg for 1-2 years, with liver function investigations, is recommended.

Contraception of Women with Epilepsy, Treatment in Pregnancy and Breast Feeding

Effective contraception needs to be applied in women suffering epilepsy in order to avoid unplanned pregnancy. Risks of getting pregnant despite contraception, as well as of short-term and long-term effects of every contraception method should be explained carefully. The risk of unsuccessful contraception in women subject to ASD enzyme inductor treatment is 3 times higher than in healthy women. In therapeutic doses less than 200 mg/day TPM does not interact with the norethisterone and ethinylestradiol-containing oral contraceptives. In higher doses (200–800 mg/day) TPM may slightly increase the ethinylestradiol clearance. In women subject to ASD enzyme inductor treatment the efficiency of oral contraceptives may be increased by increasing the dose of estrogens up to 50 µg (maximum 70 µg), decrease of the drug-free interval from 7 to 4 days and introduction of triple cycle (administration of 3 packs one after another). It is appropriate to combine with other contraception methods – barrier methods, transdermal plasters, etc. Double dose of levonorgestrel (6 mg within 120 hours after the sexual intercourse) is recommended for post-sexual intercourse contraception. Oral contraceptives may change the efficiency of some ASD – for example LTG, especially during the first 3 days of LTG monotherapy and with estrogen-containing contraceptives. There is not enough evidence for the efficiency of contraceptives containing only progesterone in women subject to ASD enzyme inductor treatment.

Risks for pregnant women:

- **Risk of multiplied seizures** (increased scope of distribution of drugs, protein link and liver metabolism) – dosage is increased as appropriate after serum level testing.
- **Risk of complications for the mother** - – preeclampsia, hyperemesis, premature birth, anemia.
- **During delivery – 1-2% of the women with epilepsy suffer seizures.**
- **Neurologist is not competent with regard to the delivery management, the type of delivery and obstetrician's behavior**

Risks for the fetus:

- **Risk of malformation** - 25% higher in women with epilepsy in comparison to general population and almost twice higher in case of anticonvulsive treatment – severe malformations (defects

of neural tube, such as spina bifida, orofacial defects, such as palatum fissum, heart malformations, hypospadias) and small malformations (hypertelorism, epicanthus, hypoplastic fingers). Ultrasound examinations of the fetus are recommended – at the beginning of pregnancy, during the 3rd, 6th and at the beginning of the 9th month, and in case of suspicion for malformation – alpha-protein test and amniocentesis.

• **Recommendations for behavior in case of pregnant and breast feeding women with epilepsy**

1. In case of women with seizures during the second half of the pregnancy that cannot be determined as epileptic seizures for sure, treatment like the one for eclampsia (magnesium sulphate) should be started until the final diagnosis clarification. MRI and CT are considered safe, and the risk for the fetus as a result of one exposure is minimal.

2. Administration of folic acid 5 mg/day before getting pregnant and at least until the end of the first trimester of the pregnancy is recommended for all women with epilepsy for the purposes of mitigating the risk of congenital anomalies. The risk of big congenital anomalies depends on the type, number and dose of ASD. LTG (less than 300 mg/day) and CBZ (less than 400 mg/day) cause the lowest risk. свързани с най-малък риск. The risk is highest upon administration of VPA (10,7/100) or polytherapy (16,8/100) in comparison to 2,3/ 100 of women without epilepsy. As reported in the registers in the United Kingdom and Ireland, the risk of monotherapy with LEV (0,7/100), is also lower than the risk of polytherapy (5,6/100). There is no sufficient evidence for the risk of monotherapy with other ASD. The risk of repeated congenital anomaly is higher (16,8/ 100) for women who already have a child with congenital anomaly.

3. The administration of VPA and polytherapy with other ASD should be minimized before conception after careful assessment of epileptologist.

4. Topiramate is contraindicated in women of childbearing potential unless there is no other alternative treatment and they are using highly effective contraception. According to recent studies, children exposed to Topiramate therapy as monotherapy during pregnancy have an approximately 3-fold higher risk of major congenital anomalies, incl. cleft palate, hypospadias and abnormalities of various organs and systems compared to a reference group not exposed to ASD. The risks of major congenital anomalies ranged from 4.3% (1.4% in the reference group) to 9.5% (3% in the reference group). A higher incidence of low birth weight (less than 2,500 grams) and low for gestational age infants has been reported with topiramate monotherapy in mothers with epilepsy. A higher incidence of newborns with Autism Spectrum Disorders, Intellectual Disability and Attention Deficiency Hyperactivity Disorder (ADHD) has been reported in mothers with epilepsy who took topiramate during pregnancy compared to children born to mothers with epilepsy, did not accept ASD.

5. All newborns of women with epilepsy treated with ASD enzyme inductors (CBZ, PHT, PB, PRM, OCBZ, TPM, ESCBZ) should administer 1 mg of vitamin K intramuscularly aimed at preventing

hemorrhagic disease of the newborn. There is no sufficient evidence for the need to administer vitamin K by women with epilepsy for the purposes of preventing hemorrhages after birth giving.

6. The administration (oral or parenteral, if necessary) of ASD should continue during delivery. There are no studies of the optimal choice of ASD in case of seizure during delivery. In case of status epilepticus, ASD of the group of benzodiazepines are the preferred choice.

7. Continuous monitoring of fetus in women with high risk of seizure during deliver as well as after a seizure occurred after birth giving is recommended.

8. Pain relief during delivery of women with epilepsy is very important for the purposes of minimizing the seizure provoking factors. Local anesthesia (epidural, spinal, combined) is safe. Diamorphine is preferred to pethidine (epileptogenic effect) as analgesia during delivery. If general anesthesia is necessary, anesthetics like pethidine, ketamine and sevoflurane should be avoided.

9. There are no counter indications for application of delivery inducing drugs to women with epilepsy who are subject to ASD treatment.

10. Women with epilepsy should be recommended to continue the administration of ASD after birth giving. The decision for breast feeding is made on individual basis, however it should be taken into account that LTG, LEV, TPM pass into mother's milk more than VPA, CBZ, PHT.

11. It is recommended to ensure support to mothers with epilepsy after birth giving, which would minimize the seizure provoking factors, such as sleep deprivation, stress, pain.

12. If the AED dose has been increase during pregnancy, it should be revised within 10 days after birth giving for the purposes of avoiding post-partum toxicity.

In case of treatment in elderly age lower doses of ASD are recommended due to the slower liver metabolism and decreased renal clearance. In elderly patients with epilepsy and with epilepsy and intellectual deficiency (IQ<70) drugs that do not affect the cognitive functions are recommended, and in case of depression – drugs not affecting the behavior (Table 14).

Table 17. ASD Effects on Cognitive Functions and Behavior

ASD	Cognitive functions	Behavior
Carbamazepine	Minimum	Mood stabilizer
Phenytoin	Injury	Unclassified
Phenobarbital	Injury	Depression
Valproate	Minimum	Mood stabilizer
Clonazepam	Injury	Mood stabilizer?
Gabapentin	Minimum	Minimum
Lamotrigine	Minimum	Minimum
Levetiracetam	Minimum	Minimum

Oxcarbazepine	Minimum	Minimum
Tiagabine	Minimum	Minimum
Topiramate	Injury	Minimum, reports for psychosis
LCM	Unknown	Minimum
BRV	Minimum	Minimum, reports for psychosis

In patients with kidney and liver failure the choice of ASD should take into account the location of ASD metabolism and excretion. Phenytoin is not recommended due to non-linear kinetics, liver autoinduction, plenty of medicinal interactions and high level of protein link. Phenytoin and valproates may cause liver disorder. Gabapentin and levetiracetam are excreted mainly through the kidneys and their dosage should take into account the kidney failure. They are applied in case of liver failure and if drug-induced etiology is possible. Lamotrigine, which is metabolized through glucuronidation can be also applied in some patients with liver failure.

Treatment of provoked seizures: Short-term treatment with benzodiazepines reduces the risk of seizures upon suspension of alcohol and delirium tremens. After acute brain stroke or neurosurgery, prophylactic treatment with ASD is necessary. ASD started after acute brain stroke should be suspended gradually. ASD treatment is conducted in case of neuroprovoked seizures with post-stroke cause.

F. Laboratory Control

- CBC (complete blood count), coagulation profile, liver and kidney functions, depending on the adverse reactions caused by the administered ASD, whenever necessary.
- **Medication monitoring** – upon clarification of the dose of VPA, CBZ and Phenytoin and then once a year monitoring, if needed (polytherapy, toxic reactions, administration of phenytoin, liver and kidney failure, forensic medical expertise), monthly follow-up of pregnant women.

G. Suspension of ASD Treatment

After a period of 2 to 5 years without seizures, the need of reduction and suspension of ASD treatment should be assessed, which is individual for every patient, depending on the type of epilepsy, the neurological and intellectual status. Idiopathic focal childhood epilepsies usually have good forecast, without subsequent recurrences. Juvenile myoclonic epilepsy is characterized with good seizure control at low doses, but with recurrences in 80-90% of patients after suspension of treatment during the first two years, which requires continuous treatment. Recurrences in adults are 40-50%, and in children – about 25%. The forecast for the risk of reoccurrences after the suspension of ASD is more favorable in patients with normal EEG after sleep deprivation and normal cerebral MRI than in patients with epileptiform or focal abnormalities in case of sleep deprivation and/or focal cortical abnormalities of MRI. Other factors for risk of reoccurrence after suspension of ASD are as follows:

- Abnormal EEG (persisting epileptiform discharges or focal abnormalities are more unfavorable)
- Abnormal cerebral MRI (especially in cortical and limbic areas)
- Type of seizures (tonic or atonic seizures are more unfavorable)
- Combination of different types of seizures
- Great number and frequency of seizures
- Prolonged existence of epilepsy before being subject to control
- Short duration of seizure-free periods.

About 75% of recurrences after ASD suspension occur during the first year, 50% - during the first 3 months. ASD should be slowly reduced, especially phenobarbital and benzodiazepines.

H. Status Epilepticus is treated in a hospital department with possibility for intensive treatment and respiratory reanimation, where electrophysiological, neuroimaging, biochemical, cerebrospinal fluid tests are performed, serum levels of drugs, radiology of lung, monitoring and supporting of life functions, including narcosis upon intubation and supporting artificial pulmonary ventilation. Measures for aggressive antiepileptic therapy and behavior typical for SE should be undertaken if seizures continue more than 10 minutes.

Outpatient treatment of SE:

- Ensuring patency of respiratory tract
- Ensuring permanent venous catheter
- **Diazepam** – intravenously 0,2 mg/kg., in children 0,3 mg/kg, rectally 0,3 mg/kg, and in children – up to 0,5 mg/kg, **Phenobarbital** 10-20 mg/kg i.m.

Hospital treatment of SE:

1. Ensuring patency of respiratory tract, support of breathing, arterial pressure and circulation, ensuring venous catheter; monitoring of body temperature, blood pressure, ECG and respiratory function.
2. Serum electrolyte investigation, complete blood count, urea, blood sugar, alkaline acid balance and blood gas analysis, liver functions, anticonvulsant levels, alcohol, toxicological screening and the respective adjustment.
3. Bolus administration of intravenous glucose (40% 60 ml), Thiamine 160 mg i.v. (in children also Vit B₆) in case of possible hypoglycemia or alcohol intoxication

4. Benzodiazepines

1. **Diazepam** – intravenously - 0,2 mg/kg (for children - 0,3 mg/kg) or rectally 5-10 mg (for children 0,5 mg/kg); repetition of dose after 30 minutes, for 1 hour – up to 60 mg, for 24 hours – up to 200 mg when ready for orotracheal intubation. Seizure mastering is proportionately dependent on the speed of Diazepam administration, however in case of quick intravenous administration there is a risk of breathing depression and arterial hypertension, which requires readiness for assisted respiration.

- **VPA (Depakine)** - 15-20 mg/kg bolus i.v. (50 mg/min.), supporting dose of 1 mg/kg/hour
- **Phenytoin** - loading - 20 mg/kg slowly i.v. (50 mg/min.), for 24 hours – up to 2000 mg; Advantage – long-lasting effect.

In case of SE continuing more than 60 minutes – introduction in narcosis (in case of intubated patient):

- **Midazolam** loading dose - 0,15-0,20 mg/kg (<0,4 mg/min.), supporting - 0,1-0,4 mg/kg/hour.
- **Tiopental Na** 5-6 mg/kg up to 500 mg slowly i.v. for 3-5 min. and supporting with 1-5 mg/kg/hour until the occurrence of EEG pattern of suppressed volleys.
- **Propofol** loading dose- 1-2 mg/kg, supporting- 3-10 mg/kg/hour.

Treatment of complications of SE: of rhabdomyolysis – supporting normal diuresis with water saline solutions to prevent kidney failure, of hyperthermia, of the cerebral edema – combination of hyperventilation with Mannitol, corticosteroids, of concomitant infections – antibiotic therapy. Supporting the cardiovascular function, in case of hypotonia– Dopamine i.v.

I. Neurosurgical Treatment - in case of therapy-resistant epilepsies and some epileptic encephalopathies in childhood. The operative treatment is aimed at removing the epileptogenic area generating the seizures or at preventing the dissemination of epileptic discharges, and in rare cases – multiple foci – localizing to a single focus.

Neurosurgical treatment of epilepsies is carried out in about 10-15% of epilepsy patients. Candidates for epileptic surgery are:

- Forms resistant to adequate therapy conducted for appropriate time period with more than 2 ASD, separately or as polytherapy;
- Specified epileptogenic area localized in “silent” cortical area (i.e. without or with relatively low risk of post-operative neurological deficiency); lack of counter indications for surgical treatment.

Epilepsies without indications for epileptic surgery are as follows:

1. Patients with many types of seizures of different brain areas, unless 1 type is not dominating and disabling. Obligatory assessment with continuous video-EEG monitoring.
2. Patients with bilateral hippocampal atrophy in MRI.
3. Patients with idiopathic (genetic) generalized epilepsies, with self-limited childhood epilepsies and most reflex epilepsies.
4. Adults with diffuse (multi lobar) and especially bilateral polymicrogyria or subcortical strip-like heterotopy

Intellectual deficiency, especially in childhood and in some syndromes, is not a counter indication for respective or palliative intervention; in many cases preventing debilitating seizures and

improving EEG (disappearance of hypersarrhythmias, the usual abnormalities in Lennox-Gastaut syndrome) even leads to improved cognitive functioning.

Neurosurgical treatment is initiated after preliminary multidisciplinary assessment based on conducted preoperative investigations as per protocol (enclosed).

Protocol

1st stage – Selection of candidates (in accordance with Schuele & Lueders, Intractable epilepsy: management and therapeutic alternatives. The Lancet Neurology, 2008,7).

2nd stage – Preoperative diagnostics

1st phase – Noninvasive investigations

1. Continuous video-EEG monitoring in specialized department of center of epilepsies – registration of seizures with EEG and video simultaneously. In some cases, ASD should be reduced and even suspended and sleep deprivation is required. In most cases, EEG is conducted in accordance with expanded electrode scheme – use of anterior temporal (temporal-basal) electrodes and temporal-posterior (retro articular) electrodes, always with ECG lead.

Interictal EEG

Major 30-minutes investigations – obligatory for all candidates

Sufficient registration of EEG in awake and sleeping condition – obligatory for all candidates – for assessment of slow-wave and epileptiform alterations (indication for localization of the lesion zone and the irritative zone)

Ictal scalp-EEG +/- sphenoidal (semi-invasive) electrodes

- ✓ In patients with TLE
- ✓ It is not obligatory in patients with unilateral TLE: with 1) clinical semiology of mesial temporal seizures; 2) interictal EEG with data for slow-wave and epileptiform activity in leads corresponding to mesial structures; 3) firm data for hippocampal pathology in MRI. It is assumed that in these patients full correlation between semiology, EEG and MRI exists and the treatment may proceed to temporal resective interventions.

Ictal scalp-EEG

All candidates require video-EEG registration of at least 3 seizures, if the patient has the same type of seizures, or more in case of medical history for several types of seizures. In most cases, monitoring for at least 24 hours is required with registration of spontaneous sleep too.

2. High definition MRI of cerebrum – in case it is performed in accordance with the so called “epilepsy protocol” according to established international standards and adapted in a specific neuroradiological center with available specialists in neuroimaging of epilepsy. In case of insufficient localization of seizures with video-EEG and MRI as per epileptic protocol, and in some cases additional MRI techniques should be used.

3. Neuropsychological investigation (it has supporting function) – lateralizes and sometimes localizes deficiency in higher cortical functions (HCF), which supplements the data for localization of epileptogenic area. Data for existing deficiency may help to determine the possible postoperative functional risk for HCF where epileptogenic area is in or close to functionally necessary cortex.

- Where the results of these investigations show full anatomical-electro-clinical correlation with regard to the localization of the epileptogenic area (for example, clinical semiology in accordance with the medical history and the video registration corresponds to mesial temporal seizures + EEG demonstrates onset of seizures in temporal leads, corresponding to mesial structures + MRI visualizes hippocampal sclerosis or another lesion in the mesial temporal structures), the treatment may proceed to limited resective intervention (for example, anterior temporal lobectomy or selective amygdalohippocampectomy in case of MTLE – the most common symptomatic therapy-resistant focal epilepsy, especially in adults).

- Where there are not enough data (for example, negative MRI), additional functional neuroimaging examinations (FDG-PET or SPECT) should be performed to identify the epileptogenic area.

1. After carrying out the PET co-registration with MRI, it increases the opportunity for more precise correlation of the interictal hypometabolism area (in PET) with the anatomic structure (in MRI).

2. Interictal and/or ictal SPECT should be performed to demonstrate the interictal hypoperfusion in the area of the epileptic focus. It is best to perform the so-called subtraction of the two separately obtained images and subsequent coregistration with MRI (SISCOM).

3. Functional MRI is required in case of visible lesions close to the eloquent cortex which are with semiologically and EEG proved epileptogenicity – for the purposes of determining the ranges of possible resection and the need of intraoperative cortical electrostimulation.

- If there is no correlation (for example, negative MRI; inconsistent with the lesion semiology of seizures; unclear ictal EEG-onset), the patient is referred for invasive preoperative investigations.

2nd phase – Invasive investigations – they comprise EEG-monitoring with intracranial electrodes and Wada-test

This phase refers to the following but not limited to the following groups of epilepsies:

- (1) TLE, where firm lateralization is missing;

- (2) double pathology (for example, hippocampal sclerosis and focal cortical dysplasia);

- (3) lesion in non-localizing EEG;

- (4) localizing interictal and/or ictal EEG, and/or functional neuroimaging in case of lack of clearly seen lesion in MRI

- **Intracranial EEG-monitoring**

Due to the existence of modern neuroimaging technologies, only 10-20% of candidates for surgery require this type of diagnosis. It is obligatory for:

- (1) Bilateral and supposedly independent temporal seizures
- (2) Extratemporal seizures with propagation to mesial temporal structures
- (3) Temporal seizures with EEG proved onset, but with negative MRI and FDG-PET
- (4) Lack of correlation between EEG-localization and MRI finding
- (5) Impossible differentiation between neocortical and mesial TLE
- (6) Lateralization/localization of seizures in specific hemisphere/brain lobe but without pathological MRI and/or functional neuroimaging (PET, SPECT) finding
- (7) Epileptogenic area in or close to the functionally necessary cerebral cortex, which also requires intraoperative cortical stimulation.

This investigation is performed with deep electrodes (stereotaxic implantation, SEEG) or with subdural electrodes (electrode grids, strips), according to the based hypothesis for the location of the epileptogenic area on the grounds of the video-EEG data. One can proceed to this stage after discussion by neurologist (who has performed the neurophysiological assessment of the patient during the first phase) and neurosurgeon with the subsequent involvement of the patient. The registration of at least one of the habitual seizures of the patient is obligatory, and testing with electrical stimulation is mandatory in order to determine the boundaries of the epileptogenic zone in case of provocation of identical seizures and the possible proximity/ overlapping with eloquent cortex.

- **Wada-test**

Intracarotid amobarbital procedure (IAP) (amobarbital or methohexital sodium /Brevital/; recently Propofol has also been used successfully) temporarily inactivates the ipsilateral cerebral hemisphere, which allows independent testing of memory and speech in the contralateral hemisphere. Irrespective of the wider use of functional MRI for determining the lateralization and localization of HCF, due to contrary data in some of the candidates, the Wada-test is the gold standard in the preoperative evaluation of HCF.

3rd phase – ***Multidisciplinary discussion of candidates for epileptic surgery***

Both after the 1st and 2nd phase, candidates for epileptic surgery are subject to discussion by a multidisciplinary team always comprising neurologists – epileptologists, neurosurgeons specialized in epileptic surgery, and if needed, neuropsychologist, logopedist, neuroradiologist, psychiatrist. Clinical, EEG, MRI data, neuropsychological tests, and other results (for example, speech functions, social

issues, etc.) are discussed in details. Potential complications are discussed with the patient/ family, especially in case of epilepsy in the dominant hemisphere.

Patients who have received opinion for operative intervention by the multidisciplinary team are always referred to specialist-epileptologist for second opinion with regard to the proposed operative intervention.

In case of concordant (coinciding) results and goals of the patient, the team and the opinion of the epileptologist, the patient is referred for the respective operative intervention.

Surgical procedures:

1. Curative = remedial (most often resective)

- **Anterior temporal lobectomy**
- **Selective amygdalohippocampectomy**
- **Lesionectomy** (removal of the epileptogenic lesion as shown by the MRI data – temporal, extratemporal)
- **“Individually adjusted” neocortical resection** – according to the EEG, MRI and functional investigation data: eloquent cortex is preserved.
- **Hemispherectomy and functional hemispherectomy**
- **Multiple subpial transection**

2. Palliative

- **Callosotomy** (total – in young patients with polymorphic attacks; anterior – in patients over 15 years old in order to avoid severe disconnection syndrome; selective posterior – in drop attacks)

Stimulation of n. Vagus (VNS) is indicated as a supplementary therapy for reduction of seizure frequency in case of drug resistant epilepsy in adults and children above 4 years of age who are not appropriate for resective epileptic surgery or where epileptic surgery is inefficient. It is recommended in focal epileptic seizures with or without secondary generalization, or generalized seizures, post-traumatic epilepsy and tuberous sclerosis, in patients with Lennox- Gastaut syndrome (good effect in generalized tonic-clonic and tonic seizures, but insignificant in atonic, myoclonic and atypical absences). Through the stimulation of n. Vagus achieves an average 50% reduction in seizure frequency in about 45%-55% of patients, with the effect improving over time (levelC).

K. Non-pharmacological methods for treatment of childhood epilepsies

- **Ketogenic diet** supplements the treatment of some therapy resistant epilepsies in childhood. It is aimed at changing the fats: carbohydrates + proteins ratio = 2:1 to 5:1. Increased values of ketone bodies may reduce the frequency of epileptic seizures. Modified ketogenic diets are also applied. They have proved effect in Dravet syndrome (SMEI), infantile spasms, myoclonic-astatic epilepsy (Doodse

syndrome), complex tuberous sclerosis and congenital metabolic defects (pyruvate-dehydrogenase deficiency, GLUT-1 deficiency).

Epileptic syndromes with possible efficiency of ketogenic diet (at least 2 scientific publications)

- Glucose transporter protein 1 (GLUT-1) deficiency
- Pyruvate-dehydrogenase deficiency
- Myoclonic-astatic epilepsy (Doodse syndrome)
- Tuberous sclerosis
- Rett syndrome
- Dravet syndrome (SMEI)
- Infantile spasms
- Children with enteral feeding

Epileptic syndromes with possible efficiency of ketogenic diet (1 scientific publication)

- Some mitochondrial diseases
- Glycogenosis type V
- Landau-Kleffner syndrome
- Lafora disease
- SSPE

Epilepsy Treatment Levels

Treatment under outpatient specialized medical care conditions is performed by specialist-neurologist or child neurologist with initial monotherapy with a drug adequate for the type of epilepsy and the epileptic seizures in optimal dose under controlled serum levels. If the first monotherapy is inefficient or in case of side reactions, the first ASD is replaced by another ASD appropriate for the type of seizures and epilepsy (2nd monotherapy). In case of inefficiency, a second and third ASD (rational polytherapy) is added, for combinations of new ASD with decision of expert commissions at the University Multispecialty Hospital of Active Treatment.

Hospital treatment is carried out in case of:

- Status epilepticus – convulsive status epilepticus is a life-threatening condition, and the non-convulsive status epilepticus determines cognitive disorders;
- Serial seizures;
- Patients with newly found epilepsy and frequent epileptic seizures;
- Newly found epilepsy in childhood requiring neuroimaging investigations and EEG under narcosis;

- Seizures become more frequent and treatment does not have any effect, which requires specialized investigations with view of the symptomatic epilepsy;
- Progressive neurological deficiency and development of dementia with view of rediagnosis of etiology;
- Patients who are not affected by outpatient treatment, including with new ASD, with medical history of status epilepticus that requires replacement of treatment in hospital;
- Patients with severe forms of multiple polymorphic seizures, progressive forms, unclassified forms, and with complications;
- Patients who require specialized investigations with view of neurosurgical treatment of epilepsy;
- Complications;
- Expert cases for clarification of diagnosis which may require suspension of treatment under medical control.

Hospital treatment of epilepsy may be carried out in neurological, child or profiled epileptologic department or clinic of neurology/ clinic (sector) of child neurology of University Hospital, depending on the gravity of the disease and its complications. Drugs of the group of “new” antiepileptic drugs are introduced in case of proved inefficiency of classical ASD, special groups of patients (children, elderly people, pregnant women, patients suffering liver or kidney failure), side reactions or organ failure.

Stabilization and entering into remission allows further outpatient control, treatment and follow-up of the patient to be performed twice a year. Epilepsy treatment is performed 2-5 years or more, depending on the type of the epilepsy/ epileptic syndrome. Suspension of treatment is undertaken by specialist-neurologist/ child neurologist.

VIII. Epilepsy and Vaccines

As a complex of prophylactic measures aimed at ensuring specific resistance to a number of serious infectious diseases, vaccines significantly contributed to the reduction of child mortality and early disability.

Risk of vaccinations. Described rare post-vaccination complications after the application of diphtheria-tetanus-pertussis (DTP) and morbilli-parotitis-rubella in large-scale population studies with total frequency of 5,2/100 000 vaccinated individuals: demyelinating processes, febrile seizures, afebrile epileptic seizures, encephalopathy and infantile spasms due to the application of the first life vaccines. Modern vaccines are manufactured with new technologies and are rather safer and more reliable.

Whole-cell pertussis vaccine may possibly cause seizures, collapse-like episodes and encephalopathy. There is increased risk of febrile seizures during the first day after the diphtheria-tetanus-pertussis (DTP) vaccine and from the 8th to the 14th day after morbilli-parotitis-rubella (MPR)

vaccine, however no increased risk of subsequent seizures and late reactions and neurological complications is found. Causal relationship between whole-cell pertussis vaccine and infantile spasms that was supposed in the past, is now considered excluded. Collapse-like (syncope) episodes have no consequences. They occur during the first 24 hours with at least 12 hours' interval as from the time of vaccination. DTP-associated seizures are of febrile nature, however there is no evidence for the role of pertussis toxin for the post-vaccination reactions. There is no connection found between the vaccination and the onset of epilepsy, infantile spasms and CNS infections.

Acellular pertussis vaccine ensures immunity but does not contain endotoxin responsible for the local reaction and fever. The application of acellular vaccine is recommended for children with chronic brain injuries (child cerebral palsy, epilepsy, mental retardation) due to the increased risk of respiratory diseases. Children who have family history of seizures should not be excluded from DTP vaccination.

The *morbilli vaccine* may possibly cause febrile seizures during the second week after the vaccination. Morbilli vaccines manufactured after 1978 with inactivated morbilli virus have less local side manifestations. No causality has been reliably found between the vaccine and the occurrence of autism. The American Academy of Pediatrics recommends applying morbilli vaccines even to children with personal or family history of seizures, as the morbilly may cause more frequent and severe complications than a febrile seizure.

No complications of epileptic seizure type have been observed with regard to vaccines against parotitis, rubella, rabies, *Haemophilus influenzae* B, hepatitis and poliomyelitis.

In summary: Vaccination with inactivated toxoid-based vaccines, bacterial antigens, protein subunits or immunogenic protein derivatives received via recombinant technologies are not contraindicated in people with neurological diseases, including epilepsy. This category includes: tetanus vaccines, diphtheria vaccines, whooping cough vaccines, poliomyelitis vaccines, hepatitis B vaccines (HCV), influenza vaccines, *Haemophilus influenzae* type b vaccines (Hib), pneumococcus and meningococcus vaccines. In Children with uncontrolled epileptic seizures, mainly with West syndrome and therapeutically resistant epilepsy vaccinations are contraindicated.

Vaccines that are currently used have excellent reliability and tolerability and significantly decrease morbidity and mortality caused by infections in children and adults. Physicians should assist their application and are well aware of the possible side effects for the purposes of seeking and finding the causality between such vaccines and the possible neurological complications.

IX. Prognosis depends on the form, susceptibility to treatment, date of occurrence, hereditary and acquired factors. In patients who are not treated or have been treated inappropriately the disease progresses with more severe and more frequent seizures. In case of favorable course of the disease (about 60-70% of cases), treatment lasts from 2 to 5 years. 20-25% of patients are “drug-resistant”,

which requires polytherapy and application of “the new” antiepileptic drugs or surgical treatment (table 15).

Table 18. Prognosis of Epilepsies

Good prognosis	Unfavorable prognosis
1. Childhood absence 2. Self-limiting childhood epilepsies: Self-limiting epilepsy with centrotemporal spikes (Rolandic), Self-limiting epilepsy with autonomic seizures (Panayiotopoulos type), Childhood occipital visual epilepsy (Gastaut type) 3. Epilepsy in elderly patients 4. Febrile seizures 5. Benign idiopathic neonatal seizures	1. West syndrome* 2. Early infancy epileptic encephalopathy* 3. Dravet syndrome* 4. Severe childhood myoclonic epilepsy* 5. Lennox-Gastaut syndrome* 6. Epilepsia partialis continua* 7. Progressive myoclonus epilepsy* 8. Juvenile myoclonus epilepsy 9. Landau-Kleffner syndrome* 10. Temporal lobe epilepsy 11. Epilepsy due to cortical dysplasia * Prognosis is unfavorable due to neurological and intellectual deficiency

X. Disability and Mortality Rate

Timely and appropriate treatment limits the progression of the disease and disability, which has health, social and economic effect. Most of the patients (simple, uncomplicated forms, early diagnosis) are treated in outpatient conditions with good effect, 25% have drug resistance and require polytherapy, combination of the new ASD and frequent hospitalizations. Medical risk is increased in case of well controlled and drug resistant epilepsies. Mortality rate is 2-4 times higher in comparison to the total population. Most common reasons are “syndrome of sudden unexpected death” (8-17%), suicide (7-22%), convulsive status epilepticus (10%), traumas during epileptic seizure (5%), reaction to drugs (3-7%) etc.

Algorithm for Diagnosis, Treatment and Follow-up of Patients with Epilepsy

I. Diagnosis of patient with epilepsy

1. General practitioner – if seizures occur:

- Prescribes CBC, biochemistry, ECG (for differential diagnosis with cardiogenic syncope)
- Refers the patient to specialist-neurologist/ child neurologist, and in case of frequent seizures – to hospital establishment

2. Specialist-neurologist/ child neurologist and outpatient care establishment:

- Medical history
- Neurological status, possible follow-up of seizures during the examination.
- Prescribes and interprets the investigations: EEG, neuroimaging investigation (CT of cerebrum or MRI of cerebrum)
- Defines “Epilepsy” diagnosis if 2 unprovoked epileptic seizures occur or in case of one seizure under the conditions of epileptiform activity in EEG, combination with deviations in the neurological status and/or pathology shown by neuroimaging examinations.
- Prescribes treatment with ASD, which is appropriate for the type of epileptic seizures/ epileptic syndrome – I monotherapy with valproates or carbamazepine, or with another ASD (oxcarbazepine, lamotrigine) if counter indications for classical ASD exist and for special groups of patients; issues protocol.
- In case of frequent epileptic seizures or inability to conduct EEG and/or neuroimaging investigation (a child who needs anesthesia) – refers the patient to a hospital establishment (Multispecialty Hospital of Active Treatment, University Multispecialty Hospital of Active Treatment).
- Upon completion of the diagnosis process, refers the patient to the general practitioner for issue of prescriptions as per the protocol and for follow-up of the patient’s somatic condition (possible side reactions).

3. Specialist-neurologist/ child neurologist in hospital care establishment

- In patients with frequent and/or severe epileptic seizures, children or patients who cannot undergo EEG and neuroimaging investigations without anesthesia due to unrest, “epilepsy” should be diagnosed after EEG, neuroimaging investigation; patients for Territorial Expert Medical Commission.
- CBC, biochemistry, ASD serum level test (of VPA, CBZ, PHT)
- Anticonvulsant treatment is conducted (intravenously or intramuscularly), anti-edematous treatment, if necessary
- Prescribes treatment with ASD, which is appropriate for the type of epileptic seizures/ epileptic syndrome – I monotherapy – Valproate or carbamazepine, or with another ASD (oxcarbazepine, lamotrigine) if counter indications for classical ASD exist and for special groups of patients.

Refers the patient for monitoring and follow-up by specialist-neurologist in outpatient establishment and by general practitioner

Follow-up of patients with epilepsy

I. General practitioner - prescribes CBC, biochemistry every 6 months and if necessary

II. Specialist-neurologist/ child neurologist and outpatient care establishment:

1. Prescribes and interprets the investigations:
 - CBC, biochemical investigation, serum level
 - EEG every 6 months in case of well-controlled epilepsy or more frequent, if necessary (frequent seizures not affected by the prescribed ASD therapy);
 - Repeated neuroimaging examination (CT of cerebrum or MRI of cerebrum) in case of progressive foci or general cerebral symptoms, head trauma.
 - In case indication exist (frequent, severe epileptic seizures) or inability to conduct EEG and/or neuroimaging investigation (a child who needs anesthesia) – refers the patient to a hospital establishment (Multispecialty Hospital of Active Treatment, University Multispecialty Hospital of Active Treatment).
 - Refers patients to the commissions at University Multispecialty Hospital of Active Treatment for new investigations, adjustment of ASD treatment, therapy with new ASD in case indications exist, depending on the type of epileptic seizures and epileptic syndrome

III. Specialist-neurologist/ child neurologist in hospital care establishment - Multispecialty Hospital of Active Treatment

1. In case of patients with frequent and/or severe epileptic seizures, ASD side reactions or organ failure, the following investigations should be performed: CBC, biochemistry serum level of valproate, carbamazepine and phenytoin at physician's discretion
2. EEG
3. Anticonvulsant treatment is conducted (intravenously or intramuscularly), anti-edematous and anti-allergic treatment, if necessary.
4. Adjusts the conducted ASD treatment (adjustment of doses), the drug combination in case of polytherapy.
5. Consults with other specialists, if necessary.
6. In case of patients referred by Territorial Expert Medical Commission, the type of epileptic seizures/ fits should be analyzed (differential diagnosis with pseudo epileptic, non-epileptic paroxysmal conditions), frequency, administered ASD (existence of serum level of ASD?), EEG.
7. In case of status epilepticus, treatment is conducted in intensive care clinic/ sector by using intravenous forms of Diazepam, Valproate, and if needed – undergoing narcosis and treatment with Tiopental, Midazolam or Propofol.

IV. Specialist-neurologist/ child neurologist in hospital care establishment – University Multispecialty Hospital of Active Treatment

1. Conducts EEG (also under anesthesia in case of young and unrest children); video EEG, if necessary; Neuroimaging investigation if the patient has not been investigated or in case of progressive disorder of neurological status)
2. Adjusts the ASD treatment, II or III monotherapy or rational polytherapy in case of patients with drug resistance, severe forms of multiple polymorphic seizures, progressive forms, unclassified forms, and medical history data for suffered status epilepticus, complications, allergic reactions, ASD side reactions and organ failure.
3. In case of status epilepticus, treatment is conducted in intensive care clinic/ sector by using intravenous forms of Diazepam, Valproate, and if needed – undergoing narcosis and treatment with Tiopental, Midazolam or Propofol.
4. Therapy-resistant patients with indications for surgical treatment of epilepsy should be referred to University Multispecialty Hospital of Active Treatment providing conditions for continuous video-EEG monitoring, neuroimaging investigations and neuropsychological investigations for the purposes of preoperative assessment (in accordance with the enclosed protocol).
5. In case of patients referred by Territorial Expert Medical Commission – analyzes the type of epileptic seizures/ fits (differential diagnosis with pseudo epileptic, non-epileptic paroxysmal conditions), frequency, administered ASD (existence of serum level of ASD), EEG.
6. A commission at the University Multispecialty Hospital of Active Treatment issues expert opinion for treatment with the new ASD and combinations of ASD based on the type of epilepsy, seizure frequency, preceding therapy, age, side reactions, and/or data for organ failure.
7. Refers the patient for monitoring and follow-up by specialist-neurologist in outpatient establishment and by general practitioner

Annexes

Figure 2. Diagnostic Process in Patients with Epileptic Seizures

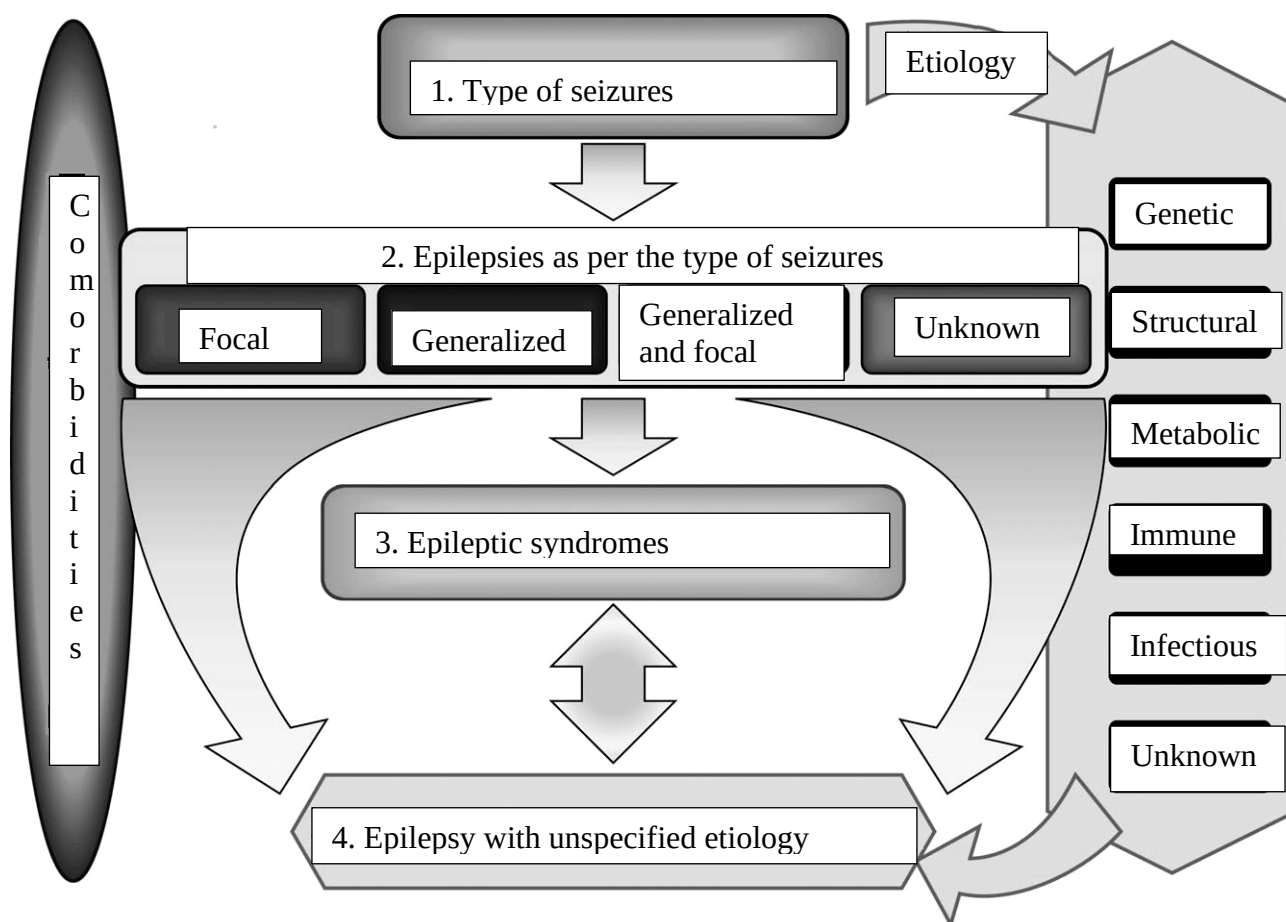
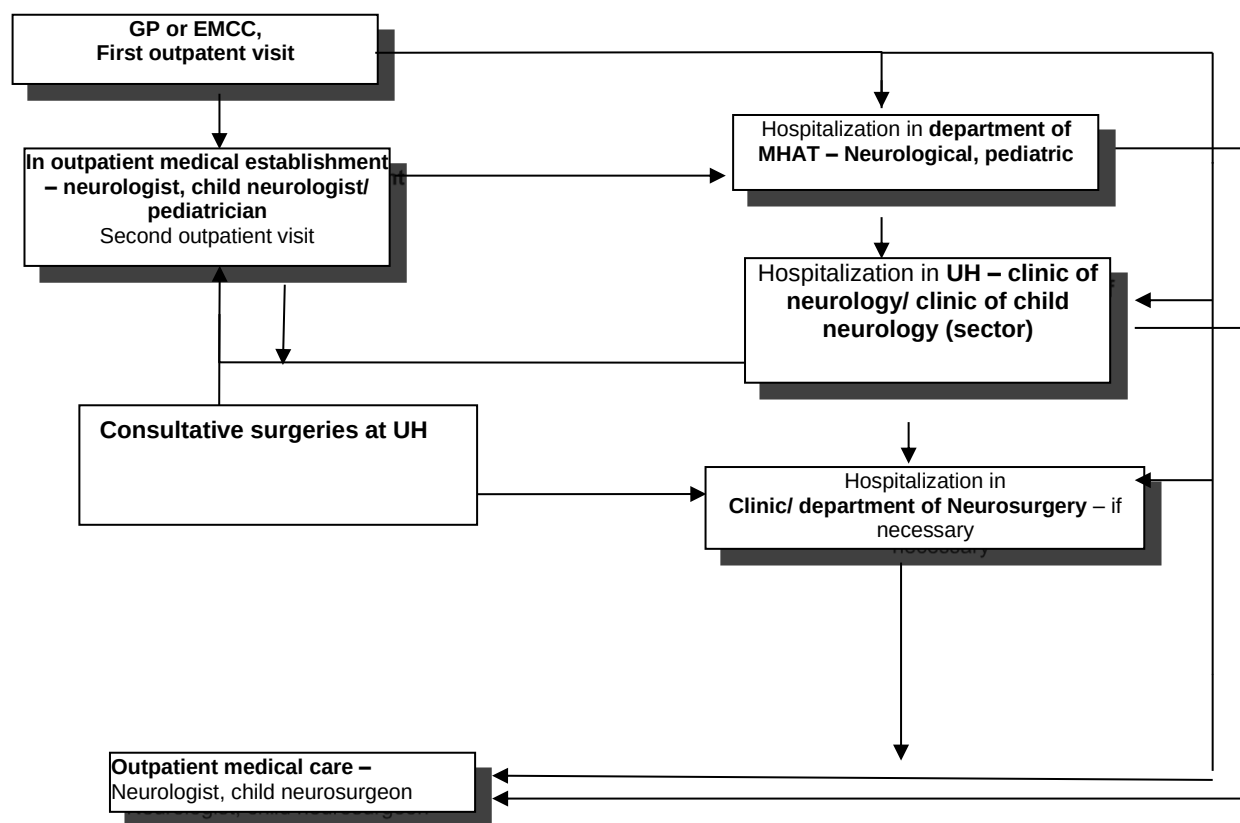


Figure 3. Patient's Roadmap



GP – General practitioner

EMCC – Emergency medical care center

UH – University hospital

MHAT – Multispecialty hospital of active treatment

*consultation with psychiatrist is necessary in case of suspected epilepsy-related psychosis or alteration of personality; hospitalization in department of psychiatry of patient with epilepsy – in case of complications caused by the epilepsy

Figure 4. Diagnostic Algorithm and Follow-up of Patients with Epilepsy

