

NATIONAL CONSENSUS STATEMENT ON THE DIAGNOSIS AND TREATMENT OF EPILEPSY

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At the initiative of the Bulgarian Society of Neurology

Today, January 22, 2026, the undersigned specialists reached a consensus statement on the diagnosis and treatment of epilepsy.

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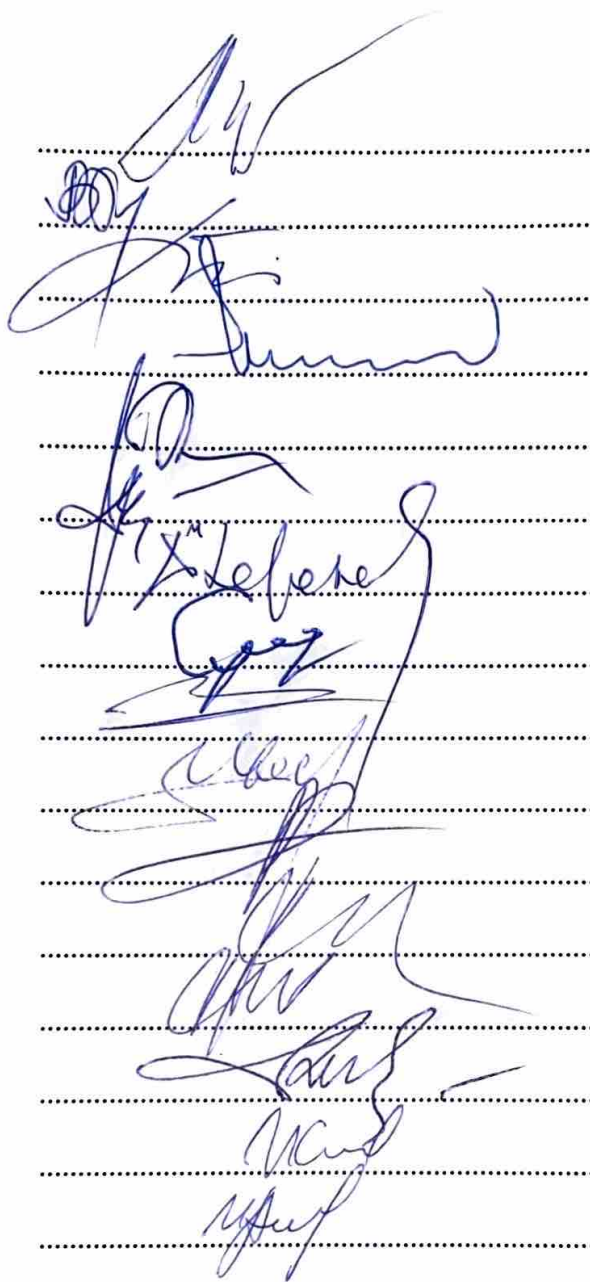


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Abbreviations

- ASDs – Anti-seizure drugs
- SGTCS - Secondary generalized tonic-clonic seizures or focal seizures evolving to bilateral tonic-clonic seizures
- GTCS - Generalized tonic-clonic seizures
- NPD - Neuropsychic development
- FBTCS - Focal seizures evolving 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
- AVM - Arteriovenous malformation
- 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
- OXC – 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 an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition”.

In 2014 ILAE expanded the definition of epilepsy to read as follows: epilepsy is a brain disorder defined under any of the following conditions:

1. At least two unprovoked (or reflex) seizures have occurred more than 24 h 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 30 days after a brain stroke, with established brain structural abnormalities and epileptiform EEG).
3. The diagnosis of epilepsy syndrome/self-limited epilepsy with centrotemporal spikes (Rolandic epilepsy) with low risk of recurring seizures, Landau-Kleffner syndrome, epileptic encephalopathy with continuous spikes and slow waves during sleep/.

Epilepsy is considered to be resolved in:

- Individuals who had an age-dependent epilepsy syndrome but are now past the typical age of the syndrome; or
- Individuals who had no seizures for at least 10 years, with no anti-seizure medicines for the last 5 years.

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

2. Epidemiology. The active epilepsy **morbidity rate** is identical in countries with different levels of economic development – 2.3-5.9/1000 for high-income countries, 3.7-13.3/1000 for upper middle-income countries, 2.4-22.8/1000 for lower middle-income countries, 3.6-15.4/1000 for low-income countries.

Morbidity rate is higher in lower middle-income countries. Average morbidity is 45 per 100,000 people in the high-income countries and 81.7 in the remaining countries.

Patients living with epilepsy in Bulgaria are about 50,000.

The onset of epilepsy in 50% to 60% of the patients is before the age of 16. Febrile seizures occur in 2% to 5% of the children under 5.

II. Epileptic seizures - definition, classification, clinical EEG characteristics

1. Definition. *Epileptic seizures* are episodes of sudden excessive and/or abnormal disruption of awareness, sensory, motor, autonomic and mental functions. Seizures are manifestation of hypersynchronous

discharge of cortical neurons. The clinical manifestation of epileptic seizures depends on the location of discharges in the cerebral cortex and their spread in the brain.

2. Classification - extended ILAE definition of epileptic seizures of 2016 and 2017. Changes include: 1. “Partial” is replaced with “focal”; 2 Seizures of unknown onset may be also classified; 3. Focal seizures are classified by alterations of awareness; 4. Classification terms such as “dyscognitive”, “simple partial”, “complex partial”, “mental”, “secondarily generalized”, “aura”, “convulsions” are abandoned.; 5 Seizures are classified as focal tonic, clonic, atonic, myoclonic, hypermotor (instead of hyperkinetic), cognitive (instead of mental, this refers also to specific expressions such as aphasia), emotional (gelastic, dacrystic), epileptic spasms, as well as their bilateral variants; 6 New 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 “secondary generalized” is replaced by “bilateral tonic-clonic”. (Fig.1)

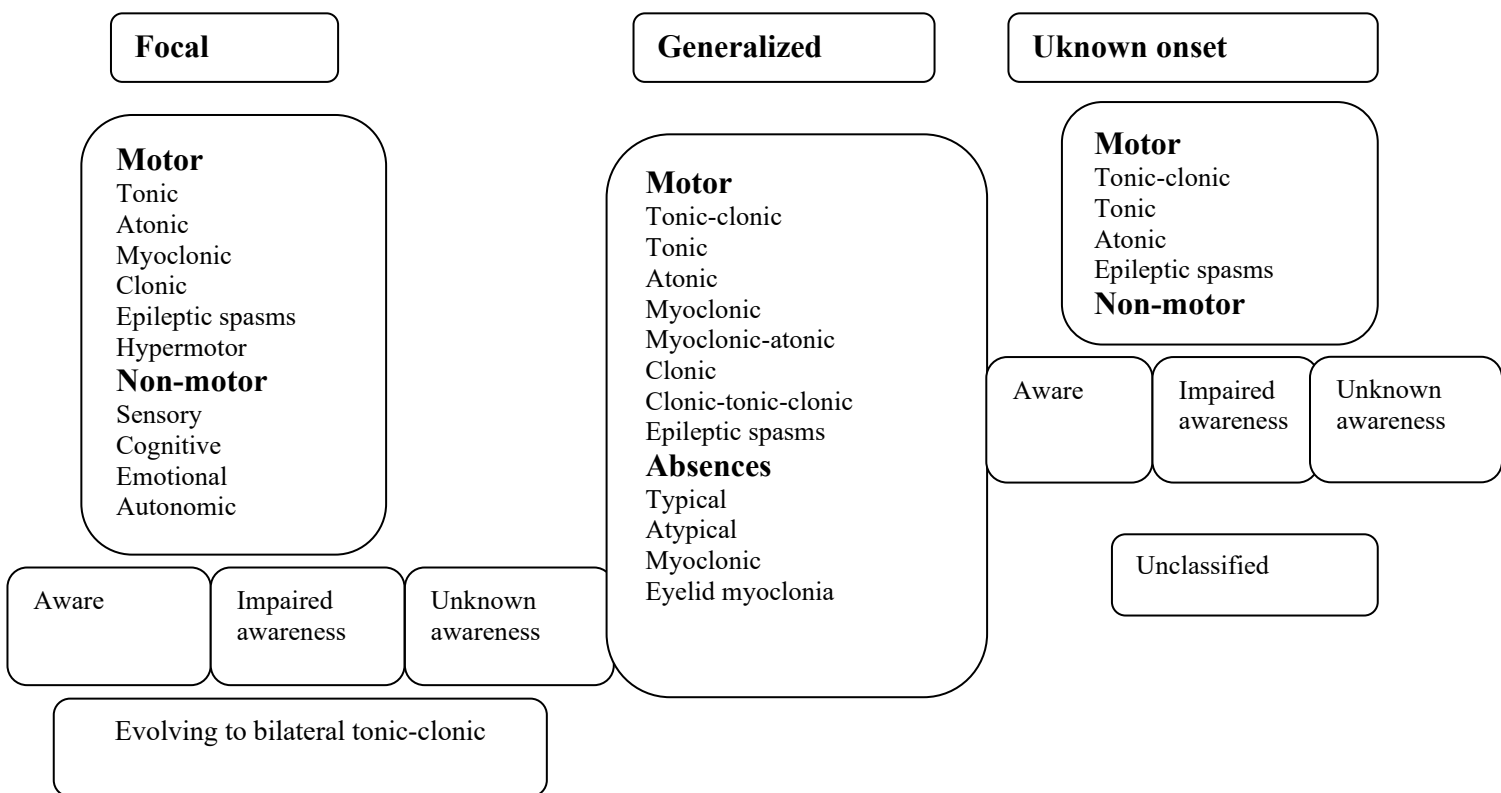


Fig. 1. Classification of epileptic seizure types (2016, 2017)

3. Clinical and EEG characteristics

Epileptic seizures are characterized as focal (partial) and generalized depending on their EEG and the clinical characteristics.

Focal seizures start from the cortical neuronal networks, in rare cases from subcortical structures (such as hypothalamic hamartoma) and remain within one hemisphere. Sometimes focal seizures are generated in more neuronal networks in both hemispheres (such as in bilateral mesial temporal lobe epilepsy, Rolandic

epilepsy). The epileptic focus is often localized by the EEG focal finding and signs. As only 40% of the seizures demonstrate correlation in the scalp EEG during seizure, clinical diagnosis is difficult.

- **Focal aware seizures** (simple partial seizures) involve motor, sensory (including odorous, gustatory and auditory), autonomic (epigastric aura with nausea, vomiting), versive with head and/or eye moving aside, and mental (paroxysmal fear or laugh). They are brief and may evolve to focal impaired awareness or directly to bilateral tonic-clonic seizures. *Differential diagnosis*: transitional ischemic attacks, hemifacial spasms and tics.
- **Focal impaired awareness seizures** (complex partial seizures) occur with a change in the level of awareness and may also evolve to bilateral tonic-clonic. They are associated with motor arrest, automatisms and postictal confusion. Focal impaired awareness seizures originating from the mesiotemporal lobes present with oro-alimentary automatisms (swallowing, lip-smacking), other automatisms (such as repetitive arm movements), dystonic phenomena and postictal confusion. Focal impaired awareness seizures originating from the frontal lobe are characterized by motor automatisms such as bicycling of the legs, etc., and quick recovery after the seizures. Focal impaired awareness seizures are associated with ictal correlation in the EEG. *Differential diagnosis*: non-epileptic seizures are characterized by a normal alpha rhythm during the behavioral alterations and impaired awareness.

Generalized seizures originate from a specific area and excitement is quickly spread over the neuronal networks, including cortical and subcortical structures. Generalized seizures may be asymmetric.

- EEG is characterized by a generalized paroxysmal activity with bilateral synchronous onset.
- Focal clinical expression is not present at the onset (only myoclonia may be asymmetric).
- Various types are distinguished (see the classification of seizures) - absence, myoclonic, clonic, generalized tonic-clonic seizures, tonic, atonic.

Absence seizures are short periods of impaired awareness (shorter than 20 sec.) without aura or post-seizure confusion, with no or rare cases of automatisms. Facial automatisms with blinking of the eyes, provoked by hyperventilation or photostimulation, are most common. Their onset is during childhood or adolescence and may subsist in adults too. They are frequently not identified in children, until a generalized tonic clonic seizure occurs. Absence seizures are characterized by an EEG showing generalized paroxysms of 3-3.5 Hz spike and slow wave discharge.

Myoclonic seizures are short, asymmetric shock-like jerks of a muscle under 1 sec., that may be grouped within several minutes and evolve to clonic seizures. The EEG is characterized by rapid polyspike-slow wave complexes.

Clonic seizures are rhythmic motor manifestations with or without impairment of awareness that may have focal origin or may be generalized, while involving both upper and lower limbs. The associated EEG presents with bilateral rhythmic epileptic firings.

Tonic seizures are characterized by a sudden tonic extension or flexion of the head, trunk and/or arms or legs lasting seconds. They usually occur out of sleep, while falling asleep or awaking. The EEG is characterized by rapid activity discharges (sharp waves, spikes) of a varying amplitude.

Tonic-clonic seizures (grand mal, GTCS) progress with motor phenomena - generalized tonic extension of the limbs lasting a few seconds, followed by rhythmic movements with continuous postictal confusion. They differ from focal seizures evolving to bilateral tonic-clonic by the absence of aura and the focal onset. The EEG during seizure shows generalized complexes of spikes or polyspikes and slow waves, often with elevated amplitude in the frontal lobes.

Atonic seizures occur with sudden reduction of postural tone that results in loss of posture (falls, injury). The EEG shows a generalized polyspike-slow wave discharge, and the loss of muscle tone confirmed by EMG coincides with the slow wave. Less frequent ictal expressions include rapid activity of varying amplitude or discharges of polyspikes, followed by generalized activity of spike-slow wave complexes.

III. Etiology and pathogenesis of epilepsy

From etiological viewpoint epilepsies are grouped into: genetic (idiopathic), structural/metabolic, autoimmune, infectious (symptomatic), of unknown etiology (cryptogenic).

1. Epilepsy is **genetic** (ILAE 2010) or idiopathic when it results from a known or suspected genetic defect, the epileptic seizures are the main symptom of the disorder, and the molecular genetic studies are the main diagnostic tests (e.g. SCN1A gene with Dravet syndrome). External factors contribute to the manifestation of the disorder. Genetic are most of the generalized epilepsies, such as infancy or juvenile epilepsy, Dravet syndrome, genetic (generalized) epilepsy with febrile seizures plus (GEFS+) (Tables 1, 3, 4) and some focal epilepsies, such as autosomal dominant front lobe epilepsy (ADNFLE), autosomal dominant partial epilepsy with auditory features (ADPEAF), etc. (Table 2, 3, 4)

Table 1. Key genes with genetic (predominantly generalized) epilepsies

	Monogenic disease	Predisposition gene
Autosomal-dominant epileptic syndromes in infancy		
Benign familial neonatal seizures	<i>KCNQ2, KCNQ3</i>	
Benign familial neonatal seizures	<i>SCN2A</i>	
Febrile seizures, GEFS+, Dravet syndrome		
GEFS+, febrile seizures, Dravet syndrome	<i>SCN1A</i>	
GEFS+	<i>SCN1B</i>	

GEFS+, febrile seizures, Dravet syndrome	<i>GABRG2</i>	
GEFS+		<i>GABRD</i>
Idiopathic generalized epilepsy		
Childhood absence epilepsy (with febrile seizures)	<i>GABRG2</i>	
Juvenile myoclonic epilepsy	<i>GABRA1</i>	
Various phenotypes	<i>CLCN2</i>	
Childhood absence epilepsy (however including other phenotypes and epileptic syndromes)		<i>CACNA1H</i>
Juvenile myoclonic epilepsy (JME) (however including other phenotypes and epileptic syndromes)		<i>EFHC1</i>

Table 2. Familial focal epileptic syndromes

	Age	Clinical presentation	Chromosome, gene
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	10 – 20 years	Nocturnal hypermotor seizures, often with retained awareness	<i>CHRNA4</i> <i>CHRNA2</i> <i>CHRNA2</i>
Autosomal dominant partial epilepsy with auditory features (ADPEAF)	20 – 40 years	Auras with auditory, dysphasic or visual features	<i>LGII</i>
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 occipito-temporal lobe epilepsy	10 – 40 years	CPS, migraine, various 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	Hemoconvulsions, often nocturnal, other partial seizures	4p15*
*Chromosomal family-specific linkage HS = Hippocampal sclerosis. FS = Febrile seizures. CPS = Complex partial seizures			

Table 3. Epileptic syndromes and genes

Phenotype (age-related)	Inheritance	Gene
Neonatal period		
Pyridoxamine 5'-phosphate oxidase deficiency (PNPOD)	AR	<i>PNPO</i>
Pyridoxine-dependent epilepsy (PDE)	AR	<i>ALDH7A1</i>
Benign and 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 syndrome (AIES)	AR	<i>ST3GAL5</i>
Early infantile epileptic encephalopathy (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, STXBPI, UBA5</i>
Dravet syndrome (DS, SMEI)	AR	<i>SCN1A, SCN9A</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, SCN1, SCN9A, STX1B</i>

Phenotype (age-related)	Inheritance	Gene
Generalized epilepsy with 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 with or without intellectual disability	AD	<i>GRIN2A</i>
Childhood absence epilepsy (CAE)	AD	<i>GABRG2</i>
	Unknown	<i>CACNA1H, GABRA1, GABRB3</i>
Adolescence and adulthood		
Junvenile absence epilepsy (JAE)	AD	<i>CLCN2, EFHC1</i>
Junvenile myoclonic epilepsy (JME)	AD	<i>CACNB4, CLCN2, EFHC1, GABRD</i>
	Unknown	<i>GABRA1</i>
Idiopathic generalized epilepsy (IGE)	AD	<i>CACNB4, CLCN2, GABRD, SLC12A5, SLC2A1</i>
	Unknown	<i>CACNA1H, CASR</i>
Adult onset familial epilepsy adult myoclonic epilepsy (FAME)	AD	<i>ADRA2B</i>
	AR	<i>CNTN2</i>
Familial temporal lobe epilepsy (FTLE)	AD	<i>CPA6, GAL, LGII</i>
<i>Unspecific age onset</i>		
Progressive myoclonic epilepsy (PME)	AD	<i>KCNC1</i>
	AR	<i>CERS1, CSTB, EPM2A, GOSR2, KCTD7, LMNB2, NHLRC1, PRDM8, PRICKLE1, SCARB2</i>
Nocturnal frontal lobe epilepsy (NFLE)	AD	<i>CHRNA2, CHRNA4, KCNT1</i>
	Unknown	<i>CHRNA2</i>
Familial focal epilepsy with variable foci (FFEVF)	AR	<i>DEPDC5</i>

Table 4. Epilepsy-associated genes

Genes	Associated epileptic syndromes
<i>ARX</i>	Infantile spasms, early infantile epileptic encephalopathy
<i>ATP1A2</i>	Benign familial neonatal convulsions, familial hemiplegic migraine and epilepsy
<i>CACNA1A</i>	Absence epilepsy and episodic ataxia, familial hemiplegic migraine
<i>CACNB4</i>	Juvenile myoclonic epilepsy
<i>CDKL5 (STK9)</i>	Infantile spasms between 3 and 6 months, neuro-mental development disorders, repetitive arm movements, atypical hypsarrhythmia (5 times more frequent in girls)
<i>CHRNA4</i>	Autosomal dominant nocturnal frontal lobe epilepsy

<i>CHRNA2</i>	Autosomal dominant nocturnal frontal lobe epilepsy
<i>CHRNA7</i>	Juvenile myoclonic epilepsy
<i>CLCN2</i>	Childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy
<i>CLTC</i>	Epileptic encephalopathy with intellectual disability
<i>DHDDS</i>	Epileptic encephalopathy with intellectual disability
<i>EFHC1</i>	Juvenile myoclonic epilepsy
<i>GABRD</i>	Genetic epilepsy with febrile seizures plus
<i>GABRA1</i>	Juvenile myoclonic epilepsy
<i>GABRB2</i>	Epileptic encephalopathy with intellectual disability
<i>GABRB3</i>	Epilepsy and autism
<i>GABRG2</i>	Childhood absence epilepsy, Genetic epilepsy with febrile seizures plus (GEFS+), Dravet syndrome (SMEI), simple febrile seizures
<i>GABBR2</i>	Epileptic encephalopathy with intellectual disability, Rett syndrome
<i>GNAO1</i>	GNAO1- epileptic encephalopathy and motor disorders
<i>KCNQ2</i>	Benign familial neonatal seizures (KCNQ2-BFNE), neonatal epileptic encephalopathies (KCNQ2-NEE)
<i>KCNQ3</i>	Benign familial neonatal seizures (BFNE), benign familial infantile epilepsy (BFIE), possible KCNQ3-related intellectual deficiency
<i>KCNMA1</i>	Generalized epilepsy with paroxysmal dyskinesias
<i>KCNT1</i>	Epilepsy of infancy with migrating focal seizures (EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).
<i>LGII</i>	Autosomal dominant partial epilepsy with auditory features
<i>NTRK2</i>	Temporal lobe epilepsy, epileptic encephalopathy with intellectual disability
<i>NUS1</i>	Epileptic encephalopathy with intellectual disability
<i>PCDH19</i>	Epilepsy in women with intellectual disability
<i>PRRT2</i>	Epilepsy, familial hemiplegic migraine, paroxysmal dyskinesia
<i>RAB11A</i>	Epileptic encephalopathy with intellectual disability
<i>SCN1A</i>	Genetic epilepsy with febrile seizures plus (GEFS+), Dravet syndrome (SMEI), familial hemiplegic migraine (FHM3)
<i>SCN1B</i>	Genetic epilepsy with febrile seizures plus (GEFS+), temporal lobe epilepsy
<i>SCN2A</i>	Genetic epilepsy with febrile seizures plus (GEFS+), early epileptic encephalopathy with neonatal onset or in childhood, benign familial neonatal/ infantile seizures

<i>SCN8A</i>	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
<i>SLC2A1</i>	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
<i>SLC25A22</i>	Early myoclonic encephalopathy, migrating partial seizures in infancy
<i>SLC35A2</i>	Early onset epileptic encephalopathy
<i>SNAP25</i>	Epileptic encephalopathy with intellectual disability
<i>ST3GAL5</i>	Epileptic encephalopathy with severe intellectual disability, choreoathetosis, scoliosis, facial dimorphism, pigmentation disorders
<i>STXBPI</i>	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.
<i>TBC1D24</i>	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 one associated with specific factors. Structural lesions are grouped into: structural lesions in acquired disorders of the central nervous system (CNS) (strokes, traumas), of genetic causes (some malformations of the cortical development, tuberous sclerosis) or 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, gangliomas, oligodendrogliomas
- Malformations of cortical development:
 - Focal cortical dysplasia
 - Hemimegalencephaly
 - Malformations of cortical development with nevi
 - Schizencephaly, lissencephalia, holoprosencephaly
 - Cortical dysplasia
 - 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** - with immune-mediated irritations of the CNS – vasculitis, autoimmune encephalitis, including Rasmussen encephalitis.
- 4. **Infectious** - with CNS infections – meningitis, encephalitis, abscesses.
- 5. **Of unknown cause (*cryptogenic*)** - epilepsy of unknown cause where genetic defect not yet established is possible. Epilepsies of genetic and unknown etiology account for about 60%, and those of structural/ metabolic etiology – for about 40%.

Other types of known etiology are to be adopted. When structural etiology is genetically predisposed, both terms – structural and genetic (such as tuberous sclerosis complex) - may be used.

Pathogenesis There is imbalance between excitement and depressive processes in neuronal populations with dysfunctions. Epileptic seizures occur due to excessive and synchronous neuronal activity disseminating in neuronal networks, engaging different sections of the cerebral cortex and/or subcortical structures and determining the seizure features.

IV. Classification of epileptic seizures

In 2010 ILAE proposed revision of the terminology, classification and concepts of epileptic seizures and syndromes, to reflect the advancement of neuroimaging technologies, fundamental studies of the mechanisms of epileptogenesis and molecular genetics. The concept of generalized and focal seizures does not apply to electro-clinical syndromes. These are classified in details in age periods of occurrence.

Classification of epilepsies by:

1. **Evolution.** The 2010 classification groups epilepsies as:

- self-limited (e.g. idiopathic focal childhood epilepsies, such as Rolandic and benign occipital epilepsies, childhood absence epilepsy in 75-80% of the cases). Spontaneous remission is typical at a specific expected age. There is no evidence of cognitive or behavioral disorders, including during the active phase of the seizures.

- drug-controlled (e.g. juvenile myoclonus epilepsy),

- drug-resistant (e.g. Dravet, West, Lennox-Gastaut syndrome). These are defined by: 1. Quantitative analysis of seizure frequency and severity (awareness disorders, contusions, long postictal dysfunction) 2. Failure to respond to treatment with ASDs consistent with the type of seizures and in appropriate doses. The last ILAE definition of 2009 provides that drug resistant patients are those who have failed an adequately administered, appropriately selected and well tolerated 2 ASDs, in monotherapy or in combination, to achieve prolonged freedom from seizures (for a period of 1 year to 3 times longer than the longest interictal period prior to the last year)” Adequate experience with ASDs means administration of a drug in an appropriate dose and for a sufficient period of time. Drug-resistant patients present with various significant adverse effects of epileptic seizures on the quality of life. When drug resistance is identified, rational polytherapy with more than 2 ASDs is required. Surgical treatment is considered if there is no positive response to the treatment and when this is indicated.

2. Electroclinical syndromes by age of onset (2017):

Neonatal period

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

Infancy

- Migrating partial seizures in infancy
- West syndrome
- Myoclonic epilepsies in infancy (MEI)
- Benign infantile seizures
- Dravet syndrome (SMEI)
- Myoclonic encephalopathies with 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 slow 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

Less specific age-related

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

Miscellaneous

- Mesial temporal lobe epilepsy with hippocampal sclerosis
- Rasmussen syndrome
- Gelastic seizures in case of hippocampal hamartomas

Conditions with non-epileptic seizures 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 revisions (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* are maintained with names. *West Syndrome* is now *Epileptic Infantile Spasm Syndrome*; *Benign childhood focal epilepsies* are now *self-limited epilepsies*: Idiopathic focal epilepsy with centrotemporal spikes (Rolandic) is renamed to Self-limited epilepsy with centrotemporal spikes; Panayiotopoulos syndrome (Benign early-onset occipital epilepsy) is renamed to Self-limited syndrome with autonomic dysfunction; Gastaut syndrome (Benign late-onset occipital epilepsy is renamed to Childhood occipital visual epilepsy; Photosensitive occipital tardive epilepsy.

The revised terminology classifies epilepsies into the following groups by age of onset (2022):

A. Epilepsies and syndromes with onset in neonates and infants (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-limited 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. Etiology-specific syndromes

1. KCNQ2- developmental encephalopathies/epileptic encephalopathies
2. Pyridoxine-related developmental encephalopathies/epileptic encephalopathies
3. Pyridoxamine-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 and epileptic encephalopathies

1. Early- infantile developmental and epileptic encephalopathy
2. Epilepsy of infancy with migrating focal seizures (EIMFS)
3. Infantile epileptic spasms syndrome (IESS)
4. Dravet syndrome.

B. Epilepsies and syndromes with onset 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-limited epilepsies:

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

II. Generalized epilepsies

1. Childhood absence epilepsy

2. Epilepsy with myoclonic absences
3. Epilepsy with eyelid myoclonia

III. Epileptic or developmental encephalopathies

1. Epilepsy with myoclonic-atonic seizures
2. Lennox–Gastaut syndrome
3. Epileptic encephalopathies or developmental encephalopathies with a spike-and-slow-wave in sleep, Landau Kleffner syndrome, atypical benign partial (focal) epilepsy in childhood
4. Hemiconvulsion–hemiplegia–epilepsy syndrome
5. Febrile infection-related epilepsy syndrome (acute encephalitis with refractory, repetitive focal seizures, or progressive epileptic encephalopathy in school-aged 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 epilepsy syndromes with polygenic etiology

1. Juvenile absence epilepsy
2. Juvenile myoclonic epilepsy
3. Epilepsy with generalized tonic–clonic seizures [GTCS]

II. Self-limited focal epilepsy syndromes with presumed complex inheritance

1. Childhood occipital visual epilepsy (COVE)
2. Photosensitive occipital lobe epilepsy (POLE)

III. Focal epilepsy syndromes with genetic, structural, or genetic–structural etiologies

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

IV. Combined generalized and focal epilepsy syndrome with polygenic etiology: epilepsy with reading-induced seizures (EwRIS).

V. Epileptic encephalopathy

1. Epilepsy syndromes with developmental encephalopathy (DE), epileptic encephalopathy (EE), or both
2. Epilepsy syndromes with progressive neurological deterioration
3. Progressive myoclonus epilepsies (PME)
4. Febrile infection-related epilepsy syndrome (FIRES)

3. By type of seizures - focal, generalized and focal epilepsy The classification of epileptic seizures and epilepsies of 2010 abandons the terms “focal and generalized epilepsy”. Most of the patients over the age of 12+ do not present with electroclinical syndrome and according to the former classification these are the patients with partial epilepsy. The 2014 revision recognizes the terms “focal and generalized epilepsy” as an appropriate description in the cases when an electroclinical syndrome cannot be identified. “Generalized and focal epilepsy” was added in 2016 to incorporate the cases with focal and generalized seizures, as well as unknown - when the type of seizure cannot be determined.

6. By etiology - see chapter III Etiology

7. Main epilepsies and epileptic syndromes. Epilepsies/epileptic syndromes are disorders characterized by similar clinical manifestations, shared pathogenesis, prognosis and treatment response. They are characterized by the type of epileptic seizures, age of onset, progression, neurological status, provoking factors, etiology, severity, family medical history, relation to sleep, EEG and prognosis, as focal (partial), generalized, reflex epilepsies, epileptic encephalopathy and conditions not diagnosed as epilepsies.

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
- Frequency - 10-11/100 000 people
- Clinical characteristics: partial seizures with Sylvian localization affecting the face, oropharynx, arm (cessation of speech, clonic flickers, paresthesia, increased salivation); Secondly generalized tonic-clonic seizures (SGTCS) or focal seizures evolving to bilateral tonic-clonic. Normal neurological status and intellect.
- EEG - unilateral or bilateral focal centrotemporal spikes, increasing during sleep.
- Treatment: Good therapeutic control - CBZ, OXC, VPA, LEV, LCM, LTG, BRV, CLZ, Clobazam, ESL, ZNS.
- Prognosis - good.

Genetic (idiopathic) occipital epilepsies. Onset - 1-14 years Normal neurological status and intellect. Epileptic seizures are versive, oculoclonic, hemiclonic, GTCS and complex partial. Two individual syndromes are distinguished depending on the age - **self-limited epilepsy with autonomic seizures** (early onset childhood occipital paroxysmal epilepsy (COPE) or Panayiotopoulos syndrome) and with late onset - **childhood occipital visual epilepsy (COVE)** (Gastaut type)

Self-limited epilepsy with autonomic seizures (early onset childhood occipital paroxysmal epilepsy (COPE) or Panayiotopoulos syndrome)

- Onset -3-6 years
- Frequency: 6% of the children up to 13 years experience single seizures mainly during sleep. 50% of the patients present with occipital paroxysms in the EEG.
- Clinical characteristics: Rare epileptic seizures, mainly during sleep (66%), with duration of 5 to 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, nausea (66%), reddening/paleness, incontinence, mydriasis, convulsions, hemiconvulsions or GTCS. Ictal syncope is possible. Visual hallucinations (up to 7%).
- EEG: Interictal - functional multifocal spike-slow wave complexes (90%); occipital paroxysms or spikes, disappearing by the age of 13 (75%), extraoccipital spikes, normal EEG, generalized discharges. Ictal EEG - usually rhythmic slow-wave activity.
- Treatment: CBZ, OXC, VPA, LCM, BRV, ESL, ZNS.
- Prognosis - *good*.

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

- Onset - after the age of 8.
- Clinical characteristics: frequent focal seizures in wakefulness, characterized by visual symptoms - elementary visual hallucinations (repetitive colors, circles) from 5-10 s up to 1-2 minutes, visual illusions (micropsia, metamorphopsia), hallucinations (10%) and blindness. Non-vision symptoms - eye deviation and tonic head (25%), symptoms of excitement propagation (less frequently) - hemiclonic (43%), complex partial seizures (14%), GTCS (13%). Postictal headache – diffuse, acute, sometimes indistinguishable from migraine, and in 10% of the patients – nausea and vomiting.
- EEG: Interictal EEG - occipital paroxysms when closing the eyes (CE). Ictal EEG - quick occipital spikes, with progressive delay and high voltage.
- Treatment: CBZ, OXC, VPA, LCM, BRV, ESL, ZNS.
- Prognosis: relatively good, remission after 2 to 4 years in 60% of the patients.

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

Temporal lobe epilepsy

- Onset in childhood.
- Major causes include tumors (DNET, gangliomas), encephalitis, mesiotemporal sclerosis, dysplasia, traumas. These are medial (mesial) epilepsies accounting for 75% (with hippocampal sclerosis or other

etiology established by MRI) and lateral (neocortical) accounting for 25%. Frequent medical history of febrile seizures.

- Clinical characteristics: The main types of seizures include simple and complex partial with or without secondary generalization and (significant) postictal confusion. Mesial localization is associated with epigastric sensations, autonomic dysfunction, psychosensory sensations (dèjà vu, jamais vu), odorous and gustatory hallucinations, visual phenomena, motor orofacial automatisms, vocalizations. The lateral (neocortical) localization is associated with sensory aphasia, vomiting and auditory symptoms. There is therapeutic resistance.

Operative treatment is considered in case of mesiotemporal sclerosis or other lesion etiology.

Frontal lobe epilepsies

- Clinical characteristics: Seizures are simple, complex partial and SGTCS mainly during sleep. Frontal seizures are brief, with minimal postictal confusion, with quick secondary generalization, prominent motor manifestations (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, epilepsia partialis continua and Todd's postictal paresis. Seizures from the additional motor cortex are hypermotor, asymmetric movements of limbs, pelvis, shoulders, head, sight deviation, vocalization, speech cessation and rhythmic repetitive movements of limbs.

Parietal lobe epilepsies are with simple focal sensory (with tenderness, 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 characteristics: Seizures are simple focal 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, OXC, LTG, LEV, TPM, LCM, BRV, ESL, ZNS, cenobamate after the age of 18, and surgical treatment.

Rasmussen syndrome

- Onset - 14 months - 14 years
- Etiology and pathogenesis - immune-mediated epileptic encephalopathy (IMEE) (presence of antibodies to GluR3 subunit of glutamate receptors, anti GluRε2 and anti-Munc18-11 in some patients).
- Histopathology - glial nodules, perivascular lymphoid infiltrations.
- Drug-resistant focal seizures, epilepsia partialis continua (60%), progressive hemiparesis;
- Progressive intellectual deficiency.
- CT and MRI-progressive cerebral hemiatrophy

- EEG - polymorph delta activity, disappearance of the normal main activity, frequent epileptiform discharges that are predominantly unilateral and may be periodic.
- Treatment: ASD, i.v. IgG and plasmapheresis with temporary success. Surgical treatment (functional hemispherectomy) is elective.

Hemiconvulsion-hemiplegia-epilepsy syndrome (HHE)

- Etiology involves infections of the central nervous system (CNS) or brain stroke.
- Onset - 5 months - 4 years (91%).
- Clinical manifestations: Stage I - HH syndrome (hemoconvulsion-hemiplegia). Stage II - HHE (hemiconvulsion-hemiplegia-epilepsy) syndrome in 80% of the cases after HH.
- Diagnosis: cerebrospinal fluid (CSF) testing, CT, MRI (edematous hemisphere with subsequent hemiatrophy).
- Treatment of epileptic status and VPA, CBZ, Clobazam, OXC, LTG, LEV, TPM, LCM, BRV, ESL, ZNZ and surgical treatment.
- Prognosis: hemiparesis, aphasia, drug-resistant partial epilepsy

2. Genetic (idiopathic) occipital epilepsies

Childhood absence epilepsy

- Genetic predisposition (multifactor)
- Onset between 3 - 10 years
- Clinical characteristics: typical absences, most often with eyelid myoclonia, with daily recurrence. Absences are often activated after photostimulation (PS) and hyperventilation (HV). More than 50% of the patients also experience GTCS during adolescence.
- EEG - ictally-generalized bilateral synchronous paroxysms of symmetric spike-slow wave complexes with frequency of 2 to 4 Hz. Normal main activity.
- Treatment - VPA, ESM, LTG, CLZ. Exacerbation is possible after CBZ, GBP, OXC, PHT, TGB and VGB, and therefore they should not be administered.
- Prognosis - good, disappearance about 20 years. Unfavorable prognosis is associated with onset before 4 and after 9 years, when there are GTCS (20%-60% of the cases).

Juvenile absence epilepsy

- Genetic predisposition
- Onset around puberty, adolescence,

- Clinical characteristics: Absences that are less frequent than in childhood absence epilepsy. About 80% of the patients also experience GTCS or absences are preceded by GTCS.
- EEG - generalized spike-slow wave complexes.
- Treatment - VPA, ESM, LTG, CLZ. Exacerbation is possible after CBZ, GBP, OXC, PHT, TGB and VGB, and therefore they should not be administered.
- Prognosis: Good follow-up when treated. May evolve to juvenile myoclonic epilepsy.

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

- Family medical history in about 40%. Autosomal-recessive, autosomal dominant inheritance.
- Onset between 8 - 18 years, most common about 15 years.
- Clinical characteristics: Myoclonic seizures, GTCS, clonic, absences, most common in the morning, after or during sleep. Absence status epilepticus. Provoking factors - sleep deprivation, photosensitivity, alcohol consumption.
- EEG: generalized spike-slow wave and polyspike-slow wave 4-6 Hz paroxysms with normal main activity and 50% of the patients - also focal abnormality or asymmetry.
- Differential diagnosis: myoclonic-astatic epilepsy (MAE) is associated with earlier onset. Progressive myoclonic epilepsies with various causes - in diseases with accumulation in the lysosomes (most often ceroid lipofuscinosis), mitochondrial diseases, Lafora and Unverricht-Lundborg diseases.
- Treatment: VPA, Clonazepam, LEV, LTG, TPM. Exacerbation is possible after VGB, TGB, CBZ, OXC, PHT, GBP, PGB, and therefore they should not be administered.
- Prognosis: recurrence in 90% of the patients if the therapy is discontinued.

Epilepsy with generalized tonic-clonic seizures on awakening.

- Onset - 9-24 years, frequency 22-37% of IGE.
- The most common seizures are GTCS within 2 hours after awakening, however absences and myoclonic seizures are also possible.
- EEG - disorganized main activity and generalized paroxysms of spike-slow wave complexes.

Myoclonic - astatic epilepsy (Doose syndrome)

- Onset between 2 - 5 years in children with normal development. Mutations in Na⁺ channel SCN1A, SCN2A and SCN1B subunits are rare.
- Clinical characteristics: The most common type of seizures are myoclonic-astatic, and absences, myoclonic, atonic, non-convulsive absence status, GTCS, and very rarely – tonic seizures are also possible.
- EEG presents with normal main activity and discharges of polyspike-slow 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-established metabolic defect), atypical benign partial epilepsies in childhood (Rolandic and Panayotopoulos type) where drop-attacks in atypical absences and negative myoclonus are possible.
- Treatment: VPA, ESM, benzodiazepines, TPM, LEV, low LTG doses, bromides, Clobazam, corticosteroids. Exacerbation after administration of CBZ, VGB, PHT is typical.
- Prognosis - unfavorable in 50% of the cases due to drug-resistant seizures, cognitive deficiency, behavioral deviations.

Epilepsy with myoclonic absences

- Rare epilepsies (0.5 - 1%) with onset between 5 months and 13 years, most common about 7 years.
- Clinical characteristics: Myoclonic (perioral, of the arms, shoulders, including asymmetric (8/60s)); GTCS, atonic, absence status. These are provoked by hyperventilation or photostimulation.
- EEG presents with brief generalized, focal or multifocal spike-slow wave or polyspike-slow wave 3Hz complexes.
- Prognosis: frequent drug resistance, cognitive deficiency, transition to juvenile myoclonic epilepsy.

Benign neonatal convulsions

- Some cases are familial, with autosomal dominant inheritance.
- Onset - 2-3 days after birth
- Clinical characteristics: Focal epileptic syndrome - brief seizures
- Normal neurological status.
- EEG - non-specific.
- Prognosis - good.

Progressive myoclonic epilepsies

- Various etiologies - diseases with accumulation in the lysosomas (most often ceroid lipofuscinosis), mitochondrial diseases, Unverricht-Lundborg disease, Lafora disease.
- Clinical characteristics: Myoclonia, epileptic seizures. Progressive neurologic deficiency.
- Prognosis: unfavorable.

3. Reflex epilepsies

These progress with reflex seizures (generalized, myoclonic or focal) caused by specific afferent stimuli: *external* (blinking lights, tactile, reading, eating) and *internal* (movements, thinking, music, calculations, decision making). Photogenically provoked seizures are the most common.

1. Genetic (idiopathic) photosensitive occipital epilepsy and other visually induced epilepsies

Intermittent photo stimulation (IPS) or other light stimulation (video games, self-induction while blinking or movements in front of the eyes) generate photoparoxysmal response (PPR), involving focal or generalized spike/polyspike-slow wave paroxysms. Photogenic seizures occur in 5 to 10% of patients with epilepsy under 18 years of age. Out of all patients with PPR 42% experience *pure photogenic epilepsy* (only photogenic seizures), 40% - spontaneous and photogenic induced seizures, and 18% - only spontaneous seizures. *Generalized epilepsies with expressed PPR* include childhood absences, juvenile absence epilepsy, juvenile myoclonic epilepsy and epilepsy with GTCS on awaking, epilepsy with eyelid myoclonia and absences (Jeavons syndrome) and Dravet syndrome.

Genetic (idiopathic) photosensitive occipital epilepsy is an age-dependent syndrome found in children with occipital epileptogenicity due to flashing lights observed in video games, TV broadcasts, disco clubs, and children with idiopathic partial or generalized epilepsy with occipital seizures.

Clinical characteristics – occipital seizures induced by photostimulation – autonomic symptoms (vomiting similar to Panayotopoulos syndrome), SGTCS, GTCS.

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

2. Startle epilepsy - it is observed in children with neurological and intellectual deficiency and other types of seizures, who experience seizures when they are startled, most frequently due to loud noise. DD - Hyperekplexia (Startle disease)

3. Reading epilepsy - it is accompanied by 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: These are characterized by:

- Delayed neuropsychic development or intellectual deficit caused by non-progressive brain damage, combined or not with epilepsy;
- Neurocognitive and behavioral deficits persist regardless of epilepsy control.

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

- Continuous epileptic activity or frequent epileptic seizures cause cognitive regression;
- Neurocognitive and behavioral abnormalities may improve with seizure control and 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 persist, even when seizures are controlled; there may be some improvement.

Epileptic encephalopathies and developmental encephalopathies are a genetically heterogeneous group where the genetically-associated loss of function or gain of function are material to the understanding of encephalopathy, etiogenesis and efficiency of therapeutic approaches. For example, pathological variants in *SCN1A* (sodium voltage-gated channel alpha subunit 1) and the impairment of the functions in sodium channel NaV1.1 provokes the Dravet syndrome and *other epileptic encephalopathies*, such as genetic epilepsy with febrile seizures plus (GEFS+), myoclonic - astatic epilepsy (Doose syndrome), epileptic encephalopathy in infancy with migrating focal seizures, epilepsy with infantile spasm (West syndrome), Lennox-Gastaut syndrome, Rett syndrome, non-syndromic epileptic encephalopathy, autistic spectrum disorders, sudden unexpected death and hemiplegic migraine. Normally, interneurons suppress brain cells to generate electric activity, however in the presence of a *SCN1A* pathological variant with loss of function, the impossibility to suppress such activity leads to epileptic seizures and ASD-agonists of the sodium channels exacerbate epileptic seizures. With less frequent *SCN1A* variants, with the gain of function neurons are directly excited, thus causing electrogenesis and epileptic seizures, and ASD agonists of the sodium channels may improve the seizures. In such cases, the new anti-seizure therapies with another mechanism of action, such as Stiripentol, Cannabidiol, Fenfluramine and the ketogenic diet, have a significant effect on the epileptic syndrome. Pathological variants are also established in the potassium-ion channels *KCNQ2* with a similar effect with exacerbation of the epileptic syndrome with a therapy with the agonists of the potassium-ion channels in case of a gene defect with loss of function, but with a good effect in case of gain of function. Similar effect is observed with agonists of potassium-ion channels in the absence of a function in case of *CACNA1A* and *GABRB 3* mutations. The specific therapeutic approaches to epileptic syndromes, including an empiric therapy, direct antagonization of the genetic effects, use of agonists in case of reduced function of the ion channel or receptor, inhibition of superactive cell signal paths, correction of the damaged protein structure, protein replacement /enzyme replacement therapy and gene therapy (ASO, CRISPR/Cas9, gene replacement therapy) are based on the knowledge of the genetic causes of developmental encephalopathies and epileptic encephalopathies.

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

Gene	Protein	Type of seizures	Syndrome	Characteristics of developmental and epileptic encephalopathies	ASD response
<i>CDKL5</i>	Kinase	Spasms, myoclonies, Tonic, tonic-clonic	CDD	Mental deficiency, motor deficiency	Resistant
<i>SCN1A</i>	Na ⁺ channel: Nav1.1	Distinct, typical GTCS in To	Dravet syndrome, GEFS+, Infantile epileptic spasms syndrome (West syndrome)	Dravet syndrome, mental deficiency, delayed neuropsychological development	Na⁺ channel agonists exacerbate
<i>KCNQ2</i> / <i>KCNQ3</i>	K ⁺ channels: K _v 7.2, K _v 7.3	Various Typical focal to SGTCS	Ohtahara-syndrome, Benign, familial neonatal seizures (BFNS)	Mental deficiency	Variable ± response to Retigabine
<i>PCDH19</i>	Protocadherin 19	Focal, To provocation		Mental deficiency, autistic spectrum disorders	
<i>SCN2A</i>	Na ⁺ channel: Nav1.2	Various, focal, myoclonic, atonic	West, Ohtahara, Lennox-Gastaut, BFNE in rare cases	Mental deficiency, delayed neuropsychological development, autistic spectrum disorders	Na⁺ channel antagonists improve or exacerbate

SCN8A	Na ⁺ channel: Na _v 1.6	Various focal, GTCS, spasms, myoclonies, absences	Syndrome with epileptic infantile spasms (West syndrome), Lennox-Gastaut syndrome	Mental deficiency, delayed neuropsychological development	Response to Na⁺ channel antagonists
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Infantile epileptic spasms syndrome (West syndrome)

- Onset - during first year, most often between 3 and 5 months. Frequency - 2-4/100 000 people
- Etiology - cryptogenic in 30%, symptomatic in about 70% (degenerative, dysmetabolic disorders, cortical dysplasias, tuberous sclerosis, hypoxia-ischemic encephalopathy, cerebral hemorrhages, infections, traumas, etc.)
- Impaired neuromental development in 75% at the onset (mental and neurological deficiency)
- Epileptic seizures – epileptic (infantile) spasms, most often of flexion type affecting the axial muscles.
- EEG – hypsarrhythmia, disorganized, with bilateral asynchronous high voltage slow waves, multifocal epileptic discharges mainly in the posterior regions of the brain, voltage depression during sleep.
- Treatment - ACTH, Vigabatrin. Alternative treatment - VPA, Nitrazepam, Topiramate. In case of hemispheric lesions, lobar or smaller malformations of the cortical development, established (through video-EEG and anatomical and clinical EEG correlations) leading to the clinical manifestation of spasms with (hemi-)hypsarrhythmia, surgery with resection of the lesions is also used.
- Prognosis: unfavorable. High mortality (5%), transition into Lennox-Gastaut syndrome or focal epilepsy (25% - 65%), cognitive deficiency (66%), motor deficiency. Normal development in only 15-30% of the cryptogenic/idiopathic cases.

Lennox-Gastaut syndrome (LGS)

- 1-2% of all cases of epilepsy
- 5-10% of childhood epilepsies.
- Onset between 2 - 7 years (Age range 1-14 years)
- Between 30% and 50% of the children with West syndrome progress to LGS.
- Between 70% and 80% are *symptomatic* - brain malformations / Lissencephaly, band heterotopia (Double cortex syndrome), bilateral perisylvian polymicrogyria, tuberous sclerosis, agenesis of corpus

callosum, posthypoxic encephalopathy, postencephalitic encephalopathy/. Up to 20% de novo mutations are idiopathic: *CHD2*, *FOXG1*, *SCN1A*, *SCN8A*, *STXBPI*, *ALG13*, *DNMI*, *GABRB3*, *IQSEC2* (Xp11.22)

- The typical LGS criteria are: 1. Polymorph, therapeutically resistant seizures - tonic, atonic, atypical absence (2 of 3 types). Epileptic spasms after West syndrome, GTCS, simple focal and myoclonic seizures are possible. 2. EEG with generalized discharges of slow spike-slow wave complexes ($< 3\text{Hz}$) in wakefulness and generalized quick rhythms ($\geq 10\text{Hz}$) during sleep. 3. Impaired intellectual functions - cognitive, behavior.
- Treatment. Complete control of the seizures is not possible. The first option for ASDs includes VPA, LTG, TPM, with ESM, LEV, CBZ, PB, Phenytoin (PHT), Clonazepam, Rufinamide, Cannabidiol in combination with Clobazam, Fenfluramine as an alternative, depending on the prevailing seizures at the time; ACTH/corticosteroid courses. Surgical treatment with resection of lesions, callosotomy and vagus nerve stimulation in case of frequent and traumatic drop attacks is also used in LGS.
- Prognosis: unfavorable. High mortality (5%), intellectual deficiency in 85% - 95% of the cases and persisting seizures in 78% to 96% of the cases, nocturnal tonic seizures being most common after puberty.

Dravet syndrome (severe myoclonic epilepsy in infancy, SMEI)

- 1% of childhood epilepsies, 80% of the cases are associated with mutations in *SCN1A*, with mutations also in *SCN1B*, *PCDH19*, *GABRA1*, *STXBPI*.
- Normal initial neuromental development.
- Epileptic syndrome – progressive, polymorphic, drug-resistant. The onset is associated with complicated febrile seizures after the age of 6 months and the following 4 typical kinds of seizures are added: 1. Generalized seizures - tonic-clonic, clonic and asymmetric tonic, clonic and hemiclonic. 2. Myoclonic seizures (80%) with onset between 1 - 5 years. 3. Atypical (40%) with onset between 1 - 12 years. 4. Complex partial seizures (46%) and SGTCS between 4 months and 4 years of age. Convulsive, myoclonic or absence status epilepticus (SE) are frequent (40%).
- Seizures are provoked by t° , photostimulation, eye movements.
- Regression in cognition (100%) and in motor development (20-60%) 1-2 years after the onset of the disease.
- Prognosis - high mortality rate up to 3 years and to 6 years in case of status epilepticus, sudden unexpected death in epilepsy (SUDEP).
- Treatment: VPA, Clonazepam, Nitrazepam, ESM, Phenobarbital (PB), LEV, bromides, Stiripentol, Cannabidiol in combination with Clobazam, Fenfluramine. CBZ, OXC, PHT, GBP, VGB, TGB, PGB and high LTG doses exacerbate epileptic seizures and should not therefore be administered.

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

Onset between 1 - 10 years, peak - 4 - 5 years.

- Characteristics: EEG with continuous spike-slow wave complexes during slow-wave sleep (CSWS), taking up more than 95% of the sleep duration. Polymorphic epileptic seizures. Neuropsychological regress – attention deficiency, hyperactivity, aggressiveness, orofacial apraxia.
- Clinical manifestations: 1/3 of the patients present with abnormal neurological status and more than 50% - with MRI-established pathology.

Development stages:

- 1. Rare nocturnal motor hemiclonic seizures; 2. CSWS, increased frequency and change in the type of epileptic seizures (*nocturnal* motor and GTCS, *daytime* typical and atypical absences, myoclonic, clonic, orofacial), cognitive and behavioral deviations. 3. Rare nocturnal GTCS, daytime atonic. 4. Improvement, including in EEG (2-7 years), with residual defect.
- Diagnosis: EEG during sleep with CSWS - spike-slow wave complexes with an >85% index. Awakefulness - frontal and temporal foci, atypical absences.
- Treatment: VPA, benzodiazepines (Clobazam, etc.), LTG, LEV, TPM (CBZ and PHT have exacerbating effect), ACTH (80 E/daily) or prednisone 2-5 mg/kg with reduction for 3 months. Surgical disconnective or resective surgery is used in certain cases of congenital or early, usually hemispheric or lobar lesions with CSWS manifestations, when the anatomic-clinical-EEG correlation is established.
- Prognosis: depending on the age at onset, duration of CSWS, duration and severity of cognitive impairment, response to the AED treatment.

Landau-Kleffner syndrome (acquired aphasia-epilepsy)

- Onset between 2 - 8 years
- Clinical characteristics: Aphasia (progressive or fluctuating in 100% of the cases), 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 less often parietal-occipital localization of spikes, spike-slow wave complexes, multifocal or *generalized* (mainly during sleep), with possible manifestation of CSWS, which determines the prognosis for cognition and intellect.
- Treatment: VPA, ESM, Clobazam, LTG, LEV, TPM, Sulthiam, BRV, ESL, ACTH or corticosteroids with initial high doses - 3 months, which determines the prognosis.
- Prognosis - from benign childhood epilepsy to epileptic encephalopathy. More favorable prognosis - with onset of aphasia after 5 years of age, brief aphasic episodes, quick EEG improvement.

5. Febrile seizures.

An age-related disease with epileptic seizures in infancy and early childhood, with body temperature above 38°C, without data for infection of the CNS (meningitis, encephalitis), metabolic disorders, intoxications, etc., not diagnosed as epilepsy.

- FS are associated with high body temperature, caused in 85-90% of the cases by upper and lower respiratory tract infections (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 brief (less than 5 min.), generalized and single for 24 hours.
- “Complicated” or “complex” FS (accounting for 30%) continue more than 15 minutes, with focal nature and/or residual paresis, or are more than two for 24 hours. They require the following examinations, such as CT, MRI, EEG, and therapy with anti-seizure medications (ASDs). MRI conducted after continuous FS is likely to establish acute hippocampal impairment and subsequent progressive atrophy and sclerosis.
- The risk of FS is 30% higher if the patient has first or second degree relatives with a medical history of FS. Delayed motor development and relatives with developmental delay.
- The risk of recurrence after the first FS is 30% - 40% in children with a FS before the age of 18 months, family history of FS and $t^{\circ} < 40^{\circ} \text{C}$ during the initial seizures.
- The risk of epilepsy after a simple FS is 1% - 2,4%, and 4,1% - 6% in case of complications.

Table 6. Differential diagnosis with febrile seizures

Febrile seizures.
Infection of the central nervous system - 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)

Contemporary definition and classification of status epilepticus (2015)

Status epilepticus (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 (Table 7).

This definition has two operational dimensions:

1. The 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 must be considered and started.

2. The time point (t_2) after which there is a risk of long-term consequences This is the time point to make a decision how aggressive the treatment should be for the purposes to avoid long-term consequences.

Both time points (t_1 and t_2) for certain type of seizures are based on animal experiments of cerebral injury.

Table 7. Time points t_1 and t_2 for different types of SE

SE type	Time point t_1 or	Time point t_2
Tonic-clonic	5 min.	30 min.
Focal with impaired awareness	10 min.	> 60 min.
Absence	10-15 min. (possible changes in future – limited available data)	Unknown

SE is most common before 5 years and after 65 years of age. In 1/3 of the cases SE occurs in case of epilepsy (treatment errors, sudden termination of treatment, intercurrent diseases, etc.), in 1/3 of the cases it is acute symptomatic (in the course of brain stroke, anoxia, cranial trauma, infection of the CNS, metabolic disorders, alcohol abstinence, tumor, drug intoxication), and in 1/3 of the cases causes remain unknown. A convulsive SE for more than 30 minutes causes CNS injuries, such as vasodilatation, blood-brain barrier impairment, elevated intracranial pressure, cerebral edema, neuronal death. SE is refractory when it exceeds 60 minutes and super refractory when it exceeds 24 hours. Mortality rates are 32% with refractory and superrefractory SE.

Four diagnostic axes for SE classification are proposed

1. Semiology

2. Etiology

3. EEG correlates

4. Age

Each patient is classified by all axes. In practice, this is rarely possible due to insufficient evidence, impossibility to conduct EEG at the SE onset or dynamics in the SE semiology and EEG findings.

1. Semiology axis

This diagnostic axis refers to the clinical manifestations of SE and is fundamental for the classification.

Two taxonomic criteria are adopted:

1. Presence or absence of noticeable motor symptoms.
2. Degree of awareness impairment (quantitative or qualitative).

Based on these two criteria, SE may be:

- **Convulsive** SE - with prominent motor symptoms.
- **Non-convulsive** SE - with absent motor symptoms.

Contemporary SE classification (semiology)

(A) With prominent motor symptoms

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

A.1.a. Generalized convulsive

A.1.b. Focal onset evolving into bilateral convulsive SE

A.1.c. Unknown whether focal or generalized

A.2. Myoclonic SE (prominent epileptic myoclonic jerks)

A.2.a. With coma

A.2.b. Without coma

A.3. Focal motor

A.3.a. Repeated focal motor seizures (including Jacksonian)

A.3.b. Epilepsia partialis continua

A.3.c. Adversive status

A.3.d. Oculoclonic status

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

A.4. Tonic status

A.5. Hyperkinetic SE

(B) Without prominent motor symptoms (NCSE)

B.1. NCSE with coma (including so-called subtle SE)

B.2. NCSE without coma

B.2.a. Generalized

B.2.a.a. Typical absence status

B.2.a.b. Atypical absence status

B.2.a.c. Myoclonic absence status

B.2.b. Focal

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

B.2.b.b. Aphasic status

B.2.b.c. With impaired awareness

B.2.c. Unknown whether focal or generalized

B.2.c.a. Autonomic SE

2. Etiology axis

Contemporary SE classification (etiology)

- Acute SE (stroke, intoxication, encephalitis, etc.)
- Remote (e.g., posttraumatic, postencephalitic, post stroke, etc.)
- Progressive (e.g., brain tumor, Lafora's disease, dementias)
- SE in defined electroclinical syndromes (West, Lennox-Gastaut, Landau-Kleffner, Ohtahara, Dravet syndrome, juvenile myoclonic epilepsy, etc.)
- SE of unknown etiology (i.e., cryptogenic)

The term "idiopathic" ("genetic") is not applicable to the underlying etiology of SE.

3. EEG correlates axis

The following features should be considered with regards to SE EEG correlates:

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

The following terminology to describe the EEG patterns is proposed:

1. **Location:** generalized, lateralized, bilateral independent, multifocal
2. **Name of the pattern:** Periodic discharges, rhythmic delta activity or spike-and-slow wave/spike-and-slow wave plus subtypes.
3. **Morphology:** sharpness, number of phases, amplitude, polarity.
4. **Time-related features:** frequency, duration, onset (sudden vs. gradual), and dynamics (evolving, fluctuating, or persisting)

5. **Modulation:** stimulus-induced vs. spontaneous.

6. **Effect of intervention (medication) on EEG findings**

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 by 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).

Salzburg consensus modified criteria for non-convulsive status epilepticus

Consensus EEG criteria for diagnosis of non-convulsive status epilepticus (NCSE) were proposed in Salzburg in 2013. Following this, in 2015 Leitingner 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 evidence, whereas the clinical symptoms suspected 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:

- Exacerbation of the condition within minutes to hours.
- Lack of significant improvement in the last minutes to hours.
- Lack of metabolic disorders or evidence of neuroimaging 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 required)

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/without fluctuation, and after considering the clinical picture, adequate antiepileptic drugs are administered and the reactivity of the patient is documented after ten minutes.

C. In case of patients with known epileptic encephalopathy

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

Age axis

Contemporary SE classification (age)

1. Neonatal (0 to 30 days)
2. Infancy (1 month to 2 years).
3. Childhood (> 2 to 12 years).
4. Adolescence and adulthood (> 12 to 59 years).
5. Elderly ($\geq$ 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.
 - Differentiation from non-epileptic seizures (pseudo epileptic seizures and syncope with anoxic seizure, panic attacks)
 - Differentiation from seizures in the course of metabolic disorders, traumas, strokes, drug intoxication, 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. Aura and neuroanatomical localization (Wolf P., Benbadis S, Dimova PS et al. Epileptic Disord. 2020;22(1):15-31)

Aura phenomena	Probable localization of epileptic activity
Affective, e.g. fear, depression, joy Anxiety (sudden, brief, intense, without contents)	Temporal Amygdala
Auditory, e.g. sounds, noises or single tones Music	Heschl's gyrus, if directed lateralizing to opposite side Temporal

Aura phenomena	Probable localization of epileptic activity
Autoscopy, i.e. perceiving a double of oneself	Parietal, probably right
Cephalic, i.e. sensation in the head, e.g. light-headedness	Frontal
Dyscognitive, i.e. disturbance of components of cognition, e.g. impaired understanding, scattered thinking, dream-like states	Temporal
Epigastric, i.e. 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, e.g. bitter, acidic or metallic taste	Temporal
Hallucinatory, i.e. composite perceptions, e.g. “hearing” and/or “seeing” people Hemineglect	Depends on involved perceptions Opposite parietal lobe
Limb pain Mnemonic, i.e. ictal dysmnesia, e.g. déjà-vu (familiarity) or jamais-vu (unfamiliarity)	Opposite postcentral gyrus, parietal operculum, insula Temporal
Olfactory, usually disagreeable odor	Temporal (mesial)
Somatosensory	Parietal, lateralizing to opposite side
Visual, e.g. 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.

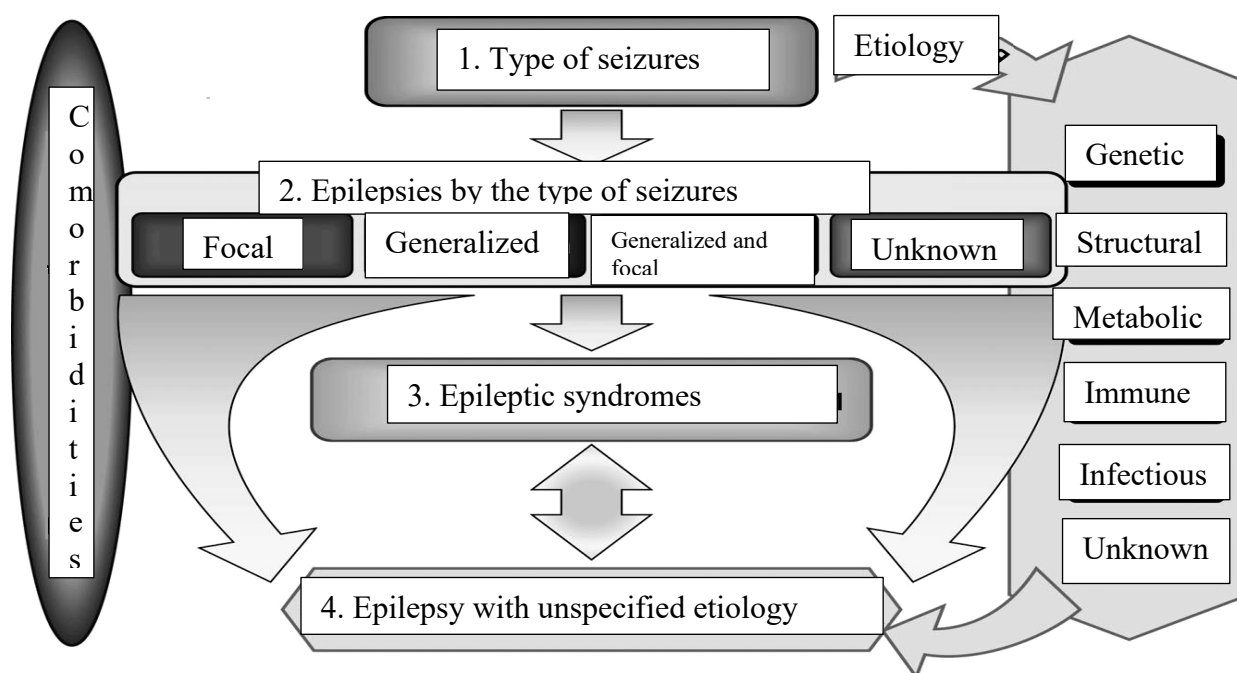


Fig. 2. Diagnostic Process in Patients with Epileptic Seizures

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 9). 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	EEG - 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 with evolution 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-slow wave complexes are possible, sometimes polyspike-slow wave, bilaterally synchronous appearing against the background of a 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-slow wave complexes, quick activity 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-slow wave complexes
Myoclonic seizures	Polyspike-slow wave and spike-slow 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 slow waves, sometimes asymmetric, often abnormal main activity
Clonic seizures	Quick activity (10 s and more) and slow waves, rarely spike-slow 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-slow wave complexes, more rarely low voltage quick activity	Polyspike-slow 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 indicates that the treatment is most likely effective.
- Epilepsy may not be diagnosed solely on the grounds of EEG epileptiform activity without the respective clinical evidence.

- **Neuroimaging investigations**

- ***Urgent:***

- Patients suffering from 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.). Contrast-enhanced CT – 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 with patients with epilepsy due to the possibility to visualize small-size lesions (cortical dysplasia and deficiency of neural migration), hippocampal sclerosis and neoplasms. It is indicated in 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 tests every 6 months.
- **ECG** of children and adults in case of suspected epilepsy and a differential diagnosis 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 (AVM), stenosis and hypoplasia of interior carotid, middle cerebral artery.
- Cerebral angiography – in case of suspicions for cerebrovascular malformations after CT, contrast-enhanced CT, MR angiography.
- Functional neuroimaging examinations – SPECT and PET for identification of local hypo-/ hyperperfusion 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 prognosis and psychological and socioeconomic issues related to epilepsy. Treatment of patients with epilepsy is carried out by specialists-neurologists and/or child neurologists. Psychiatric consultation 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 severity, better tolerance, 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 (in case of medication resistance or some specific syndromes) – neurosurgical treatment, alternative therapies (such as ketogenic diet and modifications, vagus nerve stimulation). The choice of an anti-seizure drug (ASD), the duration of therapy and the decision for hospitalization are made by specialist neurologists and/or pediatric neurologists. The treatment of epilepsy is based on some fundamental principles.

In case of **a single tonic-clonic epileptic seizure** treatment is started if there is a high risk of recurrences: EEG with interictal epileptiform abnormalities and/or persisting cause for epileptic seizures like MRI-established cortical dysplasia; 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 when the ***diagnosis is firm***: 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 less frequent than once a year or rare and slight nocturnal seizures) and in case of short-lasting focal seizures treatment is not always necessary.

A. Treatment principles

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 a *first line* ASD consistent with the type of seizures, epileptic syndrome, age of the patient, existence of comorbidities, other administered medications. The

advantages of a monotherapy comprise low toxicity, good tolerance, absence of drug interaction, minimized cognitive disorders or other adverse reactions. The effect is controlled in accordance with the clinical symptoms (frequency and severity of seizures) and by means of EEG.

3. The treatment starts with a 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 drug-resistant epilepsies (failure of two adequate ASD) – referral to specialized clinics for examinations aimed at identification of the etiology, determination and conducting of rational polytherapy and discussion for a possible neurosurgical treatment and ketogenic diet.

B. Anti-seizure Drugs (ASD)

- Modern treatment of epilepsy in children and adults is carried out with the following ASD in accordance with the registered indications as a monotherapy or a rational polytherapy, adequate for the type of epilepsy and the type of seizures, taking into account 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), Cenobamate**, Clobazam**, Clonazepam (CZP), Eslicarbazepine (ESL), Ethosuximide (ESM), Fenfluramine* (FFL), Gabapentin (GBP), Lacosamide (LCM), Lamotrigine (LTG), Levetiracetam (LEV), Nitrazepam**, Oxcarbazepine (OXC), Phenobarbital (PB), Phenytoin (PHT), Pregabalin (PGB), Rufinamide*, Stiripentol*, Sulthiam**, Tiagabine (TGB), Topiramate (TPM), Valproate (VPA), Vigabatrin (VGB)**, Zonisamide (ZNS), Methylprednisolone, Piracetam (PZT), Brivaracetam (BRV) (Tables 10, 11, 12 и 13, 14 15, 16).

* Under art. 266, para 2, of the Medicinal Products in Human Medicine Act, art. 16, para 4 of Regulation no. 10 of 2011 on the conditions and procedure of treatment with medicinal products without marketing authorisation in the Republic of Bulgaria

** Registered by the European Medicines Agency

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

C. Initial treatment of epilepsy

The treatment starts with a monotherapy with a first choice ASD drug, depending on the type of epilepsy and the type of seizures after two unprovoked seizures (Table 10), until 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 there are indications, **Lamotrigine**, are first choice drugs in case of absences.
- **Broad-spectrum ASD**, such as **Valproate**, **Lamotrigine**, **Levetiracetam**, **Topiramate**, 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 a monotherapy in case of *special conditions* (childhood – adolescence, young women and pregnant women, cognitive deficiency), adverse reactions or organ failure.

II monotherapy (alternative monotherapy) is applied in case the treatment has no effect, or in case of intolerance, adverse 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: OXC, LCM (over 4 years), ESL (over 6 years), ZNS (over 18 years).
- 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 aggravate the condition of patients with juvenile myoclonic epilepsy. In children with self-limited epilepsies (idiopathic focal epilepsies of Rolandic type, Panayotopoulos syndrome, and Gastaut type), carbamazepine and oxcarbazepine may exacerbate the condition of patients leading to 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, drug interactions)
3. Inappropriate dose, adverse 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	First choice Monotherapy	Alternative monotherapy or polytherapy
Primarily generalized (idiopathic/ genetic) epilepsies/ generalized seizures		
Tonic-clonic seizures	CBZ, PHT, VPA	CZP, LTG, LEV, OXC, PB, TGB, TPM, Clobazam**
Atonic seizures	VPA	LTG, CZP
Absences	VPA, ESM	CZP, LTG, TPM
Myoclonic seizures	VPA	CZP, ESM, LTG, LEV, TPM, Clobazam** Corticosteroids
Juvenile myoclonic epilepsy	VPA	CZP, ESM, LTG, LEV, TPM, Clobazam**
Focal epilepsies/ focal epileptic seizures		
Focal seizures	CBZ, VPA	CZP, Cenobamate**, Clobazam**, GBP, LCM, LTG, LEV, OXC, PB, PHT, PGB, TGB, TPM, BRV, ESL, ZNS
Focal seizures evolving to bilateral tonic-clonic (secondarily generalized seizures)	CBZ, PHT, VPA	CZP, Cenobamate**, Clobazam**, GBP, LCM, LTG, LEV, OXC, PB, PHT, PGB, TGB, TPM, BRV, ESL, ZNS
Idiopathic focal (Rolandic and occipital)	CBZ, VPA, OXC	CZP, GBP, LTG, LEV, Clobazam**, ZNS
Epilepsies encephalopathies / developmental encephalopathies		
Infantile epileptic spasms syndrome (West syndrome)	ACTH, VPA	CZP, LTG, TPM, VGB**
Lennox-Gastaut syndrome	LTG, TPM, VPA	CBZ, CZP, PB, PHT, Rufinamide*, Cannabidiol* with Clobazam**, Fenfluramine*
Dravet syndrome (SMEI)	VPA, TPM	LEV, Stiripentol*, Cannabidiol* with Clobazam**, Fenfluramine*
Epileptic encephalopathy with CSWS or electric status during slow-wave sleep (ESES)	VPA, ESM	LEV, benzodiazepines, Clobazam**, corticosteroids

- ASD allowed as monotherapy and supplementary therapy: **CBZ, CZP, ESM, GBP** (over 12 years – mono-, over 6 years - supplementary therapy), **ESL** (over 18 years mono-, over 6 years supplementary therapy) **LTG** (over 2 years), **LEV** (over 16 years – monotherapy, over 1 month – supplementary therapy), **LCM** (over 4 years), **OXC, PHT, PB, TPM** (over 2 years), **VPA, ZNS** over 18 years as monotherapy, over 6 years as supplementary therapy.

- **ASD only permitted as supplementary therapy: PGB** (over 18 years); **TGB** (over 12 years), where other appropriate drug combinations have proved to be unsatisfactory or are intolerable, **BRV** (over 2 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; **OXC** - oxcarbazepine; **PGB** – pregabalin; **TGB**-tiagabine; **TPM** – topiramate; **Rufinamide***- for Lennox-Gastaut syndrome; **Stiripentol***- for Dravet syndrome; **BRV** – **Brivaracetam** (over 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 focal and SGTCS (FBTCS) over 18 years; **Zonisamide** for treatment of SGTCS (FBTCS) in adults and children over 6;

*** Under art. 266, para 2, of the Medicinal Products in Human Medicine Act, art. 16, para 4 of Regulation no. 10 of 2011 on the conditions and procedure of treatment with medicinal products without marketing authorisation in the Republic of Bulgaria:**

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

*** *Stiripentol*** for treatment of Dravet syndrome

*** *Cannabidiol in combination with Clobazam***** for Dravet syndrome and Lennox-Gastaut syndrome in patients ≥ 2 years; *** *Cannabidiol*** for 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 the European Medicines Agency:**

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; **Cenobamate****- for focal and SGTCS (FBTCS) 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)	Initial 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 with VPA 0.3 with monotherapy	5-15 with enzyme inductors 5 with VPA 15 with monotherapy	50 with enzyme inductors 12.5 with VPA 25 with monotherap y	500-600 with enzyme inductors 300-400 with VPA 500 with monotherapy	700 with 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	Above 6 years 10-15	25-35	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 with monotherapy for children and adolescents above 50 kg and 8 mg/kg in children and adolescents under 50 kg; 400 mg with supplementary therapy for children and adolescents

					above 50 kg and adults
Ethosuximide	10	40	500	1500	2000
Stiripentol*	50	Up to 100	50	Up to 100	4000
Rufinamide*	Over 4 years - 10	45	400	2400	3200
Brivaracetam	- Children $\geq$ 2 years and adolescents $\geq$ 50 kg - 1 mg/kg - Over 16 years 50 - 100, divided in two equal doses	- Children $\geq$ 2 years and adolescents $\geq$ 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	Children over 6 years -10 mg/kg/day Above 60 years- 400 mg	Children over 6 years -30 mg/kg	400 once	800-1200 to 1600 mg once	1600
Clobazam**	Over 2 years - 0.4 -1 mg/kg	Titrate up to 1 mg/kg every 7 days; Under 30 kg - 20 mg; Over 30 kg - up to 40 mg	5 mg	Up to 40 mg	40 mg
Zonisamide	$\geq$ 6 years and adolescents $\geq$ 55 kg- 1 mg/kg	Titrate every 7 days to 4-8 mg/kg	100 mg	300 mg	500 mg
Cannabidiol*	$\geq$ 2 years -2.5 mg/kg twice (5mg/kg/day), titration every	LGS and Dravet syndrome - up to 10 mg/kg/day; TSC-10 mg/kg/day			LGS and Dravet syndrome - 20 mg/kg/day;

	7 days to 10-20 mg/kg				TSC – 25 mg/kg/day
Fenfluramine*	≥ 2 years - 0.2 mg/kg/day - up to 0.7 mg/kg/day maximum up to 26 mg/day	Dravet syndrome up to 0.4 mg/kg/day with Stiripentol up to 0.7 mg/kg/day without Stiripentol; LGS - 0.2 mg/kg/day - up to 0.7 mg/kg/day	0.4 mg/kg/day	Max 0.7 mg/kg/day; For DS up to 17 mg/day with Stiripentol, up to 26 mg/day without Stiripentol; LGS up to 26 mg/day	
Cenobamate**	-	-	12.5 mg once	Titration every 14 days - 25 mg, 50 mg, 100 mg, 150 mg to 200 mg	400 mg

*

Under art. 266, para 2, of the Medicinal Products in Human Medicine Act, art. 16, para 4 of Regulation no. 10 of 2011 on the conditions and procedure of treatment with medicinal products without marketing authorisation in the Republic of Bulgaria:

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

* **Stiripentol** for treatment of Dravet syndrome

* **Cannabidiol in combination with Clobazam**** for 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 the European Medicines Agency:**

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; **Cenobamate****- for focal and SGTCS (FBTCS) over 18 years, **ACTH**** for treatment of West syndrome.

Table 12. Possible aggravation of epileptic syndromes due to ASD

ASD	Syndrome	Possible aggravation
Carbamazepine	• Absence epilepsy • Juvenile myoclonic epilepsy • Progressive myoclonus epilepsies (PME) • 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 myoclonus epilepsies (PME) • 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 (rarely)	• 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 generalized tonic–clonic seizures [GTCS]	• Absences • Myoclonic seizures • GTCS
Benzodiazepines	• Lennox-Gastaut syndrome	• Tonic seizures • Absences • Myoclonic seizures

Vigabatrin	• Absence epilepsy • Epilepsy with myoclonus • Lennox-Gastaut syndrome	• Absences • Myoclonus • Focal seizures • Tonic seizures
Gabapentin	• Absence epilepsy • Epilepsy with myoclonus • Lennox-Gastaut syndrome	• Absences • Myoclonus
Lamotrigine	• Early severe myoclonic epilepsy (SMEI) • 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 patients without effect of monotherapy with 2 ASD. It is administered 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, Dravet syndrome, West syndrome, Lennox-Gastaut syndrome. When a second, respectively, third ASD is added, rational polytherapy is recommended by combining 2 (3) ASDs with different mechanisms of action (Table 11).

Some ASDs (lamotrigine, topiramate, valproic acid, zonisamide) have multiple of mechanisms of action, and other (phenytoin, carbamazepine, ethosuximide) – one main mechanism of action. ASDs 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, zonisamide, cenobamate
2. Increasing the slow inactivation of sodium channels - lacosamide
3. Increasing the GABA-A receptors - phenobarbital, benzodiazepines, clobazam, zonisamide
4. Glutamate modulators - topiramate, lamotrigine, zonisamide
5. Blockers of T- calcium channels - ethosuximide, valproate, zonisamide
6. Blockers of N- и L- calcium channels - lamotrigine, topiramate, valproate
7. H-flow modulators- gabapentin, lamotrigine
8. Blockers of different binding 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 ASD mechanisms of action

ASDs	Na⁺ channels blocking/ modulation	Ca² channels blocking/ modulation	GABA increase	Glutamate receptors blocking	Other
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					SV blocker Protein
Pregabalin		+	+		
Lacosamide	+				
Brivaracetam					SV2A protein blocker, 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-aspartate

SV2A – synaptic vesicle protein 2A

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

Depending on the registered indications the supplementary therapy includes the following new ASDs:

- **Generalized and focal seizures: LTG, LEV, TPM**
- **Focal and secondarily generalized seizures: GBP** (over 6 years), **OXC**, **PGB** (over 18 years), **LCM** (over 4 years); **BRV** (≥ 2 years); **ESL** (over 6 years); **TGB** over 12 years, where other appropriate drug combinations have proved to be unsatisfactory or intolerable. **Cenobamate - for focal SGTCS (FBTCS) ≥ 18 years; Cannabidiol** in combination with Clobazam**** for seizures

associated with tuberous sclerosis complex (TSC) in patients ≥ 2 years. **Zonisamide (ZNS)** ≥ 6 years.

- **Lennox-Gastaut syndrome** - **LTG**, **TPM**, **Rufinamide***, **Cannabidiol *** in combination with **Clobazam**** ≥ 2 years, **Fenfluramine*** ≥ 2 years.
- **Dravet syndrome (SMEI)** - **LEV**, **TPM**, **Stiripentol***, **Cannabidiol*** in combination with **Clobazam**** ≥ 2 years, **Fenfluramine*** ≥ 2 years

Table 14. Recommended combinations of ASDs for drug resistant seizures

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

* Clonazepam may be added to all ASD

E. Specificities in the administration of ASDs with various types of epilepsy in children, pregnant women and elderly patients and patients with intellectual deficit, depression, liver and kidney failure

Epilepsy in childhood. The choice of ASDs 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- /supplementing therapy	Possible mono-/supplementing therapy
West syndrome	ACTH	VPA	Benzodiazepines, TPM, VGB**
Dravet syndrome (SMEI)	VPA, TPM	Benzodiazepines, VPA	LEV, Stiripentol*, CBD* in combination with Clobazam** ≥ 2 years, Fenfluramine * ≥ 2 years
Lennox-Gastaut syndrome	VPA, VPA + LTG	LTG, TPM	Benzodiazepines, CBZ, GBP, LEV, Rufinamide* over 4 years, CBD* in combination with Clobazam** ≥ 2 years, Fenfluramine * ≥ 2 years
Epileptic encephalopathy with CSWS or electric status during slow-wave sleep (ESES)	VPA, ESM	Benzodiazepines, corticosteroids	LEV, Clobazam**
IGE with absences	VPA	LTG, ESM	Benzodiazepines
IGE with myoclonus, with or without GTCS	VPA	LTG, ESM	Benzodiazepines, LEV, PB, TPM , Clobazam**
IGE with myoclonus and GTCS	VPA	LTG, TPM	Benzodiazepines, LEV, PB, Clobazam**
IGE with GTCS	VPA	LTG, TPM	LEV, PB, Benzodiazepines, Clobazam**
Focal	CBZ, OXC, VPA	LTG, TPM, GBP	LEV, PB, LCM ≥ 4 years, BRV ≥ 2 years, ESL ≥ 6 years, ZNS $\geq$ 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***** for 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 the European Medicines Agency:**

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; **Cenobamate****- for focal and SGTCS (FBTCS) over 18 years, **ACTH**** for treatment of West syndrome.

Table 16. Types of registered ASDs for monotherapy and supplementary therapy with indications, including for childhood

ASD	Monotherapy	Supplementing therapy
Valproate (10-50 mg/kg)	Absences, GTCS, focal, SGTCS	Absences, GTCS, focal, SGTCS (FBTCS)
Carbamazepine (10-20 mg/kg)	focal, SGTCS	GTCS, focal, SGTCS (FBTCS)
Ethosuximide (15-30 mg/kg)	Absences	
Phenytoin (3-8 mg/kg)	GTCS, focal, SGTCS	GTCS, focal, SGTCS (FBTCS)
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 (FBTCS); over 12 years-myoclonic seizures in juvenile myoclonic epilepsy and GTCS
Oxcarbazepine (30-46 mg/kg)	Over 6 years focal and SGTCS	Over 6 years - supplementary therapy for focal seizures and SGTCS (FBTCS)
Brivaracetam (1-4 mg/kg)	-	Over 2 years - supplementary therapy for focal and SGTCS (FBTCS)
Gabapentin (40 mg/kg)	Above Over 12 years - focal seizures	Over 6 years - supplementary therapy for focal seizures
Lacosamide (8-10 mg/kg)	At and over 4 years - monotherapy for focal seizures	Over 4 years - supplementary therapy for focal seizures
Tiagabine (0.1-1 mg/kg)	-	Over 12 years - supplementary therapy for focal seizures
Eslicarbazepine (10-30 mg/kg)	Over 18 years focal and SGTCS	Over 6 years - supplementary therapy for focal and SGTCS (FBTCS)
Vigabatrin** from 4 mg/kg titration up 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 up to 5 - 10 mg/kg	-	Rolandic epilepsy after failure of other ASD; focal seizures and SGTCS (FBTCS), 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 years and adolescents	-	Focal and SGTCS ≥ 6 years

≥ 55 kg- 1 mg/kg titration to 8 mg/kg		
Cannabidiol* 5 mg/kg/day, titration up 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 years- 0.2 mg/kg- to 0.7 mg/kg maximum to 26 mg/day	-	Dravet Syndrome, Lennox-Gastaut Syndrome
Felbamate** from 15 mg/kg titration up 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.)

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* *Rufinamide* for treatment of Lennox-Gastaut syndrome

* *Stiripentol* for treatment of Dravet syndrome

* *Cannabidiol in combination with Clobazam*** for 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 the European Medicines Agency:**

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; **Cenobamate****- for focal and SGTCS (FBTCS) over 18 years, **ACTH**** for treatment of West syndrome.

Treatment of Febrile Seizures (FS)

1. Acute treatment of febrile seizures includes treatment of the underlying disease and prolonged FS as in status epilepticus with Diazepam 0.3–0.5 mg/kg rectally or intravenously. Antipyretic treatment with Paracetamol (Acetaminophen) and Ibuprofen does not reduce the risk of recurrent FS, but improves the child's general condition by lowering the fever.

2. Prophylaxis treatment Intermittent prophylaxis with Diazepam or constant treatment with Valproate is recommended, depending on the risk of recurring FS. Simple FS do not need treatment. Intermittent prophylaxis of FS with Diazepam curbs the risk of recurring FS. Continuous treatment of FS with anticonvulsive drugs does not prevent the risk of epilepsy.

- **Intermittent prophylaxis with rectally or orally administered Diazepam** is recommended for FS with onset before 1 year; family medical history of FS in one of the parents; 2 or more FS or frequent FS (2 within 12 hours, 3 within 6 months or 4 within 1 year): Diazepam - 0.3-0.5 mg/kg rectally if $t^{\circ} > 37.5^{\circ} \text{C}$ every 12 hours (therapeutic plasma concentration after 2-4 min.) or orally administered Diazepam - 0.3 mg/kg every 8 hours (therapeutic plasma concentration after 30-90 min.) until 24 without fever are achieved . (therapy for up to 3 days).
- **In case of high risk of recurring FS** (combination of complicated prolonged FS > 15 min., neurological deficiency, age up to 1 year, frequent FS, FS in the first hour of febrile illness or $t^{\circ} < 38^{\circ}$), continuous prophylaxis treatment with Valproate 30 mg/kg for 1-2 years is recommended, with liver function tests.

Contraception in women with epilepsy, treatment during pregnancy and breastfeeding

Women with epilepsy must be offered efficient contraception to avoid undesired pregnancy. Despite contraception, the risk of pregnancy, as well as for the short- and long-term adverse effects of each method of contraception must be carefully explained. The risk of unsuccessful contraception with women undergoing treatment with ASD enzyme inductors is three times higher than with healthy women. In therapeutic doses under 200 mg/day of TPM does not interact with orally administered contraceptives, containing norethisterone and ethinylestradiol. Higher doses of TPM (200–800 mg/day) may insignificantly increase the clearance of ethinylestradiol. In women undergoing treatment with ASD enzyme inductors the effect of orally administered contraceptives may increase with increase of the dose of estrogens to 50 μg (max 70 μg), reduction of the drug-free interval from 7 to 4 days and introduction of a triple cycle (administration of 3 packs in a row). Combination with other contraception methods, such as barrier methods, transdermal plasters, etc., is appropriate. A double dose of levonorgestrel (6 mg within 120 hours after intercourse) is recommended for contraception after intercourse. Orally administered contraceptives may influence the efficiency of some ASD, e.g. LTG, especially in the first three days of a LTG monotherapy and with estrogen-containing contraceptives. There is insufficient evidence of the efficiency of contraceptives only containing progesterone in women undergoing treatment with ASD-enzyme inductors.

Risks for pregnant women:

- **Risk of more frequent seizures** (increased scope of distribution of drugs, protein binding and liver metabolism) – the increase of the dosage is assessed after serum level testing.
- **Risk of complications for the mother** - preeclampsia, hyperemesis, premature birth, anemia.
- **During birth delivery** – 1-2% of women with epilepsy experience seizures.
- **The neurologist does not interfere with the birth delivery, type of delivery and obstetrician approach.**

Risks for the fetus:

- **Risk of malformations** - 25% higher in women with epilepsy than the general population and almost twice higher in case of treatment with anticonvulsive drugs – severe malformations (defects of neural tube, such as *spina bifida*, orofacial defects, such as *palatum fissum*, heart malformations, hypospadias) and minor malformations (hypertelorism, epicanthus, hypoplastic fingers). Ultrasound examinations of the fetus are recommended – at the beginning of pregnancy, in 3rd, 6th and at the beginning of the 9th month, and in case of suspicion for malformation – alpha-protein test and amniocentesis.

- **Recommended actions for pregnant and breastfeeding women with epilepsy**

1. Women with seizures occurring during the second half of pregnancy, which cannot be readily diagnosed as epilepsy, must start treatment as if for eclampsia (magnesium sulphate) until determination of the diagnosis. MRI and CT are considered harmless and the risk of one-time exposure for the fetus is minimum.

2. All women with epilepsy are recommended to take 5mg/day of folic acid prior conception and at least until the end of the first trimester of pregnancy in order to reduce the risk of congenital abnormalities. The risk of major congenital abnormalities depends on the ASD type, number and dose. LTG (less than 300 mg/day) and CBZ (less 400 mg/day) are associated with the lowest risk. The highest risk is associated with the administration of VPA (10.7/100) or polytherapy (16.8/100), compared to 23/100 in women without epilepsy. According to the UK and Irish registers, the risk during monotherapy with LEV (0,7/100) is also lower compared to polytherapy (5.6/100). There is insufficient evidence for the risk during monotherapy with other ASDs. The risk of recurring congenital abnormality is higher (16.8/100) in women who already have a child with congenital abnormalities.

3. The administration of VPA and polytherapy with other ASD must be minimized prior conception, after a careful evaluation by a epileptologist.

4. A therapy with Topiramate is contraindicated in women of childbearing potential, unless there is no other alternative treatment and if they use highly-efficient contraceptives. The most recent studies demonstrate that children exposed to a therapy with Topiramate as a monotherapy during pregnancy are exposed to a three-

fold increased risk of major congenital abnormalities, including cleft palate, hypospadias and abnormalities of various organs and systems compared to a reference group not exposed to ASD. The risks of major congenital abnormalities are between 4.3% (1.4% in the reference group) to 9.5% (3% in the reference group). Higher incidence of newborns with low birth weight (<2500 g) and lower weight for the gestational age is reported in case of monotherapy with Topiramate administered to women with epilepsy. Higher incidence of newborns with autistic spectrum disorders, intellectual disability and attention deficit hyperactivity disorder (ADHD) are reported in women with epilepsy, who have followed a therapy with Topiramate during pregnancy, compared to children born by women with epilepsy, who have not taken ASDs.

5. All newborns of women with epilepsy treated with ASD enzyme inducers (CBZ, PHT, PB, PRM, OXC, TPM, ESL) must take 1 mg of vitamin K intramuscularly to prevent hemorrhagic disease of the newborn. There is insufficient evidence of the need to administer vitamin K in women with epilepsy to prevent postbirth haemorrhages.

6. The administration (orally or parenterally) of ASDs must continue during birth delivery. There are no studies for the optimum choice of a ASD in case of a seizure during birth delivery. ASDs of the benzodiazepine group are preferred in case of status epilepticus.

7. Continuous monitoring of the fetus in women with a higher risk of seizure during delivery, as well as after a seizure during delivery, is recommended.

8. Pain relieving in women with epilepsy is very important to minimize seizure-provoking factors. Local anesthesia (epidural, spinal, combined) is safe. Diamorphine is preferred to pethidine (epileptogenic effect) as an analgesic during birth delivery. If general anesthesia is needed, anesthetics such as pethidine, ketamine и sevoflurane should be avoided.

9. There are no contraindications to the administration of delivery-inducing medications in women with epilepsy undergoing treatment with ASDs.

10. Women with epilepsy are recommended to continue the ASD therapy after birth. The breastfeeding decision is individual, however it should be considered that LTG, LEV, TPM enter to a greater extent into mother's milk than VPA, CBZ, PHT.

11. Mothers with epilepsy need support after birth in order to minimize seizure-provoking factors, such as sleep deprivation, stress, pain.

12. If the ASD dose was increased during pregnancy, it must be revised within 10 days after birth to avoid postpartum toxicity.

Treatment in elderly age is recommended to include lower ASD doses due to delayed liver metabolism and lowered renal clearance. Elderly patients with epilepsy and epilepsy and intellectual disability

(IQ<70) are recommended to take drugs that do not affect cognitive functions, and in case of depression - drugs not affecting their behavior (Table 17).

Table 17. ASD effects on cognitive functions and behavior

ASD	Cognitive functions	Behavior
Carbamazepine	Minimum	Mood stabilizer
Phenytoin	Impairment	Unclassified
Phenobarbital	Impairment	Depression
Valproate	Minimum	Mood stabilizer
Clonazepam	Impairment	Mood stabilizer?
Gabapentin	Minimum	Minimum
Lamotrigine	Minimum	Minimum
Levetiracetam	Minimum	Minimum
Oxcarbazepine	Minimum	Minimum
Tiagabine	Minimum	Minimum
Topiramate	Impairment	Minimum, reports of psychosis
LCM	Unknown	Minimum
BRV	Minimum	Minimum, reports of psychosis

In case of patients with renal and liver failure, the choice of ASDs takes into consideration the location of ASD metabolism and excretion. Phenytoin is not recommended due to non-linear kinetics, liver autoinduction, multiple drug interactions and high degree of protein binding. Phenytoin and valproates may cause liver damage. Gabapentin and levetiracetam are mainly excreted through kidneys and their dose takes renal failure into account. These are administered in case of renal failure and in case of possible drug-induced etiology. Lamotrigine, which is metabolized by glucuronidation can be also used in some patients with liver failure.

Treatment of provoked seizures Short-term treatment with benzodiazepines reduces the risk of seizures from termination of alcohol consumption and delirium tremens. Preventive treatment with ASDs is not necessary after an acute brain stroke or neurosurgery. ASDs started after an acute brain stroke are gradually excluded. Treatment with ASDs is administered in case of unprovoked seizures with a post-stroke cause.

F. Laboratory control

- CBC, coagulation profile, liver and renal functions, depending on the adverse reactions caused by the administered ASD, when necessary

- **Medication monitoring** – upon determination of the VPA, CBZ and Phenytoin dose and then yearly thereafter and when necessary (polytherapy, toxic reactions, administration of phenytoin, liver and kidney failure, forensic medical expertise), monthly follow-up of pregnant women.

G. Termination of ASDs treatment

After a period of 2 to 5 years without seizures, assessment of the need of reduction or termination of ASD treatment that is individual for each patient depending on the type of epilepsy, neurological and intellectual status. Idiopathic focal childhood epilepsies usually have a good prognosis and without recurrences. Juvenile myoclonic epilepsy involves good control of seizures and low doses, however with recurrence in 80-90% after termination of treatment in the first two years and requires long-term treatment. Recurrences are 40-50% in adults and about 25% in children. The recurrence risk prognosis is more favorable after termination of ASDs in patients with a normal EEG after sleep deprivation and a normal brain MRI scan than in patients with epileptiform or focal abnormalities after sleep deprivation and/or focal cortical abnormalities established in the MRI scan. Other factors for risk of recurrence after ASD termination include:

- Abnormal EEG (more unfavorable are persisting epileptiform discharges or focal abnormalities).
- Abnormal brain MRI (especially cortical and limbic areas)
- Type of seizures (more unfavorable are tonic or atonic seizures)
- Combination of different types of seizures
- Multiple seizures and frequency of seizures
- Long history of epilepsy before being put under control
- Short periods without seizures

About 75% of recurrences after termination of ASDs are during the first year and 50% - in the first three months. ASDs are reduced slowly, especially phenobarbital and benzodiazepines.

H. Treatment of status epilepticus is made in a unit, which allows intensive care and breathing resuscitation, where electrophysiological, neuroimaging, biochemical, CSF, drug serum level tests, lung X-ray examinations are made and the life supporting functions are monitored and supported, including narcosis in case of intubation and mechanical ventilation. Measures for aggressive antiepileptic treatment and behavior as if with SE are undertaken if the seizures continue for more than 10 minutes.

Pre-hospital SE treatment must:

- Ensure patency of airways
- Ensure permanent venous catheter
- **Diazepam**– i.v. 0.2 mg/kg., children - 0.3 mg/kg, per rectum - 0.3 mg/kg, children up to 0.5 mg/kg, **Phenobarbital** 10-20 mg/kg i.m.

Hospital SE treatment must:

1. Ensure patency of airways, support breathing, arterial pressure and circulation, provide venous catheter; monitor body temperature, blood pressure, ECG and breathing function.
2. Test serum electrolytes, complete blood picture, urea, blood sugar, acid-base balance and blood gas analysis, liver functions, levels of anticonvulsive drugs, alcohol, perform toxicological screening and make the relevant adjustment.
3. Include bolus introduction of glucose (40% 60 ml), Thiamine 160 mg i.v. (children: including Vit B₆) in case of possible hypoglycemia and intoxication.

4. Benzodiazepines

- **Diazepam** – i.v. - 0.2 mg/kg (children: 0.3 mg/kg) or per rectum 5-10 mg (children: 0.5 mg/kg); repeated dose after 30 min, for 1 hour - up to 60 mg, for 24 hours - up to 200 mg, maintaining readiness for orotracheal intubation. Seizure control proportionately depends on the speed of administration of Diazepam, however the quick administration contains a risk of breathing depression and arterial hypotension, which may require assisted respiration.
- **VPA (Depakine)** - 15-20 mg/kg bolus i.v. (50 mg/min), maintenance 1 mg/kg/hour.
- **Phenytoin** - induction dose - 20 mg/kg slow i.v. (50 mg/min), for 24 hours - up to 2000 mg; Advantage - long-lasting effect.

SE continuing more than 60 minutes - narcosis (with intubated patients):

- **Midazolam** induction dose - 0.15-0.20 mg/kg (<0.4 mg/min.), maintenance dose - 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 maintenance with 1-5 mg/kg/hour until EEG pattern of burst suppression.
- **Propofol** induction dose - 1-2 mg/kg, maintenance dose - 3-10 mg/kg/hour.

Treatment of SE complications: rhabdomyolysis - maintenance of normal diuresis with water saline solutions to prevent renal failure, hyperthermia, brain edema - combination with hyperventilation with Mannitol, corticosteroids, accompanying infections - antibiotic therapy. Maintenance of cardiovascular function, in case of hypotension - Dopamine i.v.

I. Neurosurgical treatment - in case of therapy-resistant epilepsies and some epileptic childhood encephalopathies. The purpose of surgical treatment is to remove epileptogenic area that generates the seizures or to prevent the dissemination of epileptic discharges, and in rare cases with multiple foci - reduction to a single focus.

Neurosurgical treatment of epilepsies is conducted in 10-15% of patients diagnosed with epilepsy. Epilepsy surgery is applied with:

- Forms that are resistant to an adequate therapy administered for an appropriate period of time, with more than two ASDs used individually or as a polytherapy;
- Identified epileptogenic area in a 'silent' cortical area (i.e. without or with a relatively low risk of postoperative neurological deficiency); absence of contraindications to surgical treatment.

Epilepsy surgery is not indicated in the following cases:

1. Patients with many types of seizures in various areas of the brain, unless one type is prevalent and leads to disability. Obligatory assessment with a continuous video-EEG monitoring is required.
2. Patients with bilateral hippocampal atrophy in the MRI scan
3. Patients with idiopathic (genetic) generalized epilepsies, with self-limited childhood epilepsies and most reflex epilepsies.
4. Adults with diffuse (multilobar) and especially bilateral polymicrogyria (PMG) or subcortical band heterotopia (SBH).

Intellectual deficiency, especially in childhood and with some syndromes, is not a contraindication to resective or palliative intervention. In many cases the prevention of seizures leading to disability and the improvement of EEG (disappearance of hypersarrhythmia, usual abnormalities associated with the Lennox-Gastaut syndrome) leads to improved cognitive functioning.

Neurosurgical treatment is performed after a preliminary multidisciplinary evaluation based on protocol-based tests before the surgery (annexed)

Protocol

Stage I - Selection of candidates (as per Schuele & Lueders, Intractable epilepsy: management and therapeutic alternatives. The Lancet Neurology, 2008,7).

Stage II - Intraoperative diagnosis

Phase 1 - Non-invasive tests

1. Continuous video-EEG monitoring in a specialized unit of an epilepsy center - simultaneously EEG and video registration of seizures. Some cases require reduction of the dose or termination of ASDs or sleep deprivation. Expanded electrode EEG scheme is conducted in most cases - using the anterior temporal (temporobasal) electrodes and temporoposterior (retroauricular) electrodes, in any case with ECG leading.

Interictal EEG

Basic 30-minute examination - obligatory for all candidates

Sufficient registration of EEG in wakefulness and during sleep - obligatory for all candidates - to evaluate the slow-wave and epileptiform alterations (direction of the localization of the lesion zone and irritative zone).

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

- ✓ Patients with TLE
- ✓ Not obligatory in patients with unilateral TLE with 1) clinical semiology of mesiotemporal seizures; 2) interictal EEG with evidence of slow-wave and epileptiform activity in the leads, consistent with the mesial structures; 3) firm evidence of hippocampal pathology in the MRI scan. With such patients it is assumed that there is complete correlation between semiology, EEG and MRI and temporal resective interventions may be undertaken.

Ictal scalp EEG

All candidates need video EEG registration of at least three seizures if the patient suffers from one type, or of more if the medical history indicates several types of seizures. Monitoring for at least 24 hours, including registration of spontaneous sleep, is required in most cases.

2. High-resolution MRI scan of the brain - if performed in compliance with the epilepsy protocol according to the internationally adopted standards and adjusted in a specific neuroradiology center with specialists in epilepsy neuroimaging. In case of insufficient localization of the seizures with video-EEG and MRI in compliance with the epilepsy protocol, additional MRI techniques are required.

3. Neuropsychological examination (which has a supplementary meaning) - lateralizes and sometimes localizes deficiency in the higher cortical functions, which supplements the evidence of the localization of the epileptogenic zone. The evidence of the present deficiencies may support the determination of the possible post-operative functional risk for the higher cortical functions, when the epileptogenic zone is in or close to the functionally necessary cortex.

- When the results of these examinations demonstrate full anatomical-electro-clinical correlation with regard to the localization of the epileptogenic area (for example, clinical semiology is in accordance with the medical history and the video registration is consistent with mesial temporal seizures and EEG demonstrates onset of seizures in temporal leads, corresponding to the mesial structures, and MRI presents evidence of hippocampal sclerosis or other lesion in the mesial temporal structures), limited resective intervention may be undertaken (for example, anterior temporal lobectomy or selective amygdalohippocampectomy in case of MTLE – the most common symptomatic therapy-resistant focal epilepsy, especially in adults).

- If there is insufficient evidence (for example, negative MRI), additional functional neuroimaging examinations (FDG-PET or SPECT) should be performed to identify the epileptogenic area.

1. The PET scan co-registration with MRI increases the probability of more precise correlation of the interictal hypometabolism area (in PET) with the anatomic structure (in MRI).

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

3. Functional MRI scan is required in case of prominent lesions close to the eloquent cortex which are with semiologically and EEG established epileptogenicity – in order to determine the boundaries of possible resection and the need of intraoperative cortical electrostimulation.

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

2nd phase – Invasive examinations – they include EEG-monitoring with intracranial electrodes and Wada-test.

It refers but is not limited to the following group of epilepsies:

- (1) TLE, where there is no firm lateralization;
- (2) double pathology (such as hippocampal sclerosis and focal cortical dysplasia);
- (3) lesion with non-localizing EEG;
- (4) localizing interictal and/or ictal EEG and/or functional neuroimaging in the absence of a clearly visible lesion on the MRI scan.

- **Intracranial EEG monitoring**

In view of the availability of modern neuroimaging technologies, only 10-20% of candidates for surgery require this type of diagnosis. It is obligatory for:

- (1) Bilateral seizures and temporal seizures that are suspected for being independent
- (2) Extratemporal seizures propagating to the mesiotemporal structures.
- (3) Temporal seizures with established EEG onset, however with negative MRI and FDG-PET.
- (4) No correlation between EEG-localization and the MRI findings.
- (5) Impossible differentiation between the neocortical and mesial TLE.
- (6) Lateralization/localization of the seizures in a certain hemisphere/brain area, however without pathological findings in the MRI scan and/or functional neuroimaging (PET, SPECT)
- (7) Eliptogenic area in or close to the functionally required cortex, which requires also intraoperative cortical stimulation.

It is performed with deep electrodes (stereotaxic implantation, SEEG) or with subdural electrodes (electrode arrays, bands), consistent with the underlying hypothesis for the location of the eliptogenic area on the grounds of the video-EEG evidence. Neurological consultation (with the neurologist who performed the neurophysiological assessment of the patient during the first phase) and neurosurgical consultation are required to proceed to this stage, with subsequent involvement of the patient. At least one of the habitual seizures of the patient must be registered. Electrical stimulation testing is mandatory 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 to determine the lateralization and localization of the higher cortical functions, due to contradictory data in some of the candidates, the Wada-test is the gold standard in the preoperative evaluation of higher cortical functions.

Phase 3 - *Multidisciplinary assessment of candidates for epilepsy surgery*

Both after the 1st and 2nd phase, candidates for epileptic surgery are assessed by a multidisciplinary team always comprising neurologists – epileptologists, neurosurgeons specialized in epilepsy surgery, and if needed, neuropsychologists, speech therapists, neuroradiologists, psychiatrists. Clinical, EEG, MRI data, neuropsychological tests, and other results (for example, speech functions, social issues, etc.) are discussed in detail. Potential complications are discussed with the patient/family, especially in case of epilepsy in the dominant hemisphere.

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

If the results and objectives of the patient, the team and the opinion of the epileptologist overlap, the patient is referred for the respective operative intervention.

Surgical procedures:

1. Curative, i.e. remedial (most often resective)

- **Anterior temporal lobectomy**
- **Selective amygdalohippocampectomy**
- **Lesionectomy** (resection of the epileptogenic lesion as shown by the MRI data – temporal, extratemporal)
- **Patient-individualized neocortical resection** – according to the EEG, MRI and functional examinations data: the eloquent cortex is preserved.
- **Hemispherectomy and functional hemispherotomy**
- **Multiple subpial transection**

2. Palliative

- **Callosotomy** (total – in young patients with polymorphic attacks; anterior – in patients over 15 years in order to avoid severe disconnection syndrome; selective posterior – in drop attacks)
- **Vagus nerve stimulation (VNS)** is indicated as a supplementary therapy for reduction of seizure frequency in case of drug-resistant epilepsy in adults and children over 4 years of age who are not appropriate for resective epilepsy surgery or where epilepsy 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). The Vagus nerve stimulation reduces the frequency of seizures averagely by 50% in about 45%-55% of the patients and the effect improves over time (level C).

J. Non-pharmacological medical treatment in childhood epilepsies

- The **ketogenic diet** supplements the treatment of some therapy-resistant epilepsies in childhood. Its objective is to change fats: carbohydrates + proteins ratio from 2:1 to 5:1. Higher values of ketone bodies may reduce the frequency of epileptic seizures. Modified ketogenic diets are also used. The effect of the diet has been observed with the Dravet syndrome (SMEI), infantile spasms, myoclonic-astatic epilepsy (Doose 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 (Doose syndrome)
- Tuberous sclerosis
- Rett syndrome
- Dravet syndrome (SMEI)
- Infantile spasms
- Children on enteral feeding

Epileptic syndromes with possible efficiency of ketogenic diet (at least 1 scientific publications)

- Some mitochondrial diseases
- Type V glycogenosis
- Landau-Kleffner syndrome
- Lafora disease
- SSPE

Epilepsy treatment levels

Treatment in outpatient specialized medical care conditions is performed by a neurology specialist or a pediatric neurologist with the initial monotherapy with a drug consistent with the type of epilepsy and the epileptic seizures in optimal dose, provided that controlled serum levels are under control. If the first monotherapy is not efficient or adverse reactions occur, the first ASD is substituted by another that is consistent with the type of seizures and epilepsy (II monotherapy). Second or third ASD (rational polytherapy) may be added if the treatment is not efficient, and combinations of the new ASDs may be used with a resolution of the panel of experts at the University Multispecialty Hospitals of Active Treatment.

Hospital treatment is administered for:

- **Status epilepticus** - the convulsive one is life-threatening, and the non-convulsive provokes cognitive impairments.
- Serial seizures;
- Patients with newly diagnosed epilepsy and frequent epileptic seizures.
- Newly-established childhood epilepsy which requires neuroimaging investigations and EEG under narcosis.
- Increased incidence of seizures and lack of response to the treatment, which necessitates specialized examinations in view of the symptomatic epilepsy.
- Progressive neurological deficiency and development of dementia, for the prospect of early repeated diagnosis of the etiology.
- Patients with no response to outpatient treatment, including with the new ASDs, with status epilepticus in the medical history, where change of treatment in hospital conditions is required.
- Patients with severe types of multiple polymorph seizures, progressive forms, unclassified forms and with complications.
- Patients who need specialized examinations for the prospect of neurosurgical treatment of epilepsy.
- Complications.
- Diagnosis clarification cases where termination of the treatment under medical control may be required.

Hospital treatment of epilepsy may be carried out in neurological, pediatric or specialized epilepsy department or neurology clinic / pediatric neurology clinic (sector) of the university hospital, depending on the severity of the disease and its complications. New antiepileptic drugs are introduced when the standard ASDs are inefficient or for special groups of patients (children, elderly people, pregnant women, patients with liver or kidney failure), adverse reactions or organ failure.

Stabilization and remission allow further outpatient control, treatment and follow up of the patient twice a year. Epilepsy treatment takes up to 2 - 5 years or more, depending on the type of epilepsy or epileptic syndrome. Termination of the treatment is undertaken by a neurology specialist/pediatric neurologist.

VIII. Epilepsy and vaccines

As a set of preventive measures, immunizations are aimed at creating a specific resistance to a series of serious infectious diseases and have contributed to reduce children mortality and early disability.

Risk of immunizations Reported rare post-vaccination complications after diphtheria-tetanus-pertussis (DTP) and morbilli-parotitis-rubella in large-scale population studies with total frequency of 5.2 per 100 000 vaccinated individuals: demyelinating processes, febrile seizures, afebrile epileptic seizures, encephalopathy and infantile spasms due to the application of the first life vaccines. Contemporary vaccines are produced by new technologies and are significantly safer and more reliable.

Whole-cell pertussis vaccine may cause seizures, collapse-like episodes and encephalopathy. There is an increased risk of febrile seizures in the first day after the diphtheria-tetanus-pertussis (DTP) vaccine and from the 8th to the 14th day after morbilli-parotitis-rubella (MPR) vaccine. Nevertheless, no increased risk of subsequent seizures and late reactions and neurological complications is found. The cause-effect relationship between whole-cell pertussis vaccine and infantile spasms suspected in the past is excluded nowadays. Collapse-like (syncope) episodes have no consequences. They occur within 24 hours, with at least 12-hour interval from the time the vaccine is administered. Convulsions associated with DTP have febrile characteristics, however there is no evidence of the role of pertussis toxin for the postvaccinal reactions. No link has been found between the immunization and the onset of the epilepsy, infantile spasms and infection of the central nervous system.

Acellular pertussis vaccine ensures immunity but it does not contain endotoxin, which is 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 with family medical history of seizures should not be excluded from DTP vaccination schedule.

The *morbilli vaccine* may cause febrile seizures during the second week after the vaccination. Morbilli vaccines manufactured after 1978 with an inactivated morbilli virus have less local adverse effects. No cause-effect relationship has been reliably found between the vaccine and the occurrence of autism. The American Academy of Pediatrics recommends using morbilli vaccines even for children with personal or family history of seizures, as morbilli may cause more frequent and severe complications than a febrile seizure.

No complications of epileptic seizure type have been observed as a result of vaccines against parotitis, rubella, rabies, *Haemophilus influenzae* B, hepatitis and poliomyelitis.

Summary: Vaccinations with inactivated toxoid-based vaccines, bacterial antigens, protein or immunogenic subunits, protein derivatives obtained by recombinant technologies are not contraindicated for children with neurological diseases, including epilepsy. This category includes: tetanus, diphtheria, pertussis, poliomyelitis, hepatitis B (HBV), influenza, Haemophilus influenzae type b (Hib), pneumococcus and meningococcal vaccines.

Vaccinations are contraindicated for children with uncontrolled epileptic seizures, mainly with West syndrome and therapeutically resistant epilepsy.

The currently used vaccines have excellent reliability and tolerability, considerably lower morbidity and mortality caused by infections in children and adults. Physicians must cooperate for their use and are well aware of the possible adverse effects and must seek and find the cause-effect relationship between them and the possible neurological complications.

IX. The **prognosis** depends on the type, susceptibility to treatment, history, inherited 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), the treatment lasts from 2 to 5 years. Between 20% and 25% of patients are “drug-resistant”, which requires polytherapy and application of the new antiepileptic drugs or surgical treatment (table 18).

Table 18. Prognosis with epilepsies

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

X. Disability and mortality rate

The timely and accurate treatment limits the progression of the disease and the disability, which has a health, social and economic effect. The prevailing part of the patients (simple types without complications, early diagnosed) are treated outpatiently with a good effect, 25% present with drug-resistance and require polytherapy, combinations of new ASDs and frequent hospitalizations. The medical risk is higher in well controlled and drug-resistant epilepsies. Mortality is 2 to 4 times higher than the general population. The most common are the sudden unexpected death syndrome (8-17%), suicides (7-22%), convulsive status epilepticus (10%), traumas during epileptic seizures (5%), drug reactions (3-7%), etc.

Algorithm for diagnosis, treatment and follow-up of patients with epilepsy

I. Diagnosing an epileptic patient

1. General practitioner - in case of seizures:

- Prescribes CBC, biochemistry, ECG tests (for differential diagnosis with cardiogenic syncope)
- Refers the patient to a neurology specialist, pediatric neurologist and in case of frequent seizures - to a hospital.

2. Neurology specialist/pediatric neurologist in outpatient medical care (OMC):

- Elicits medical history
- Takes neurological status, possibly monitors a seizure during examination.
- Prescribes and interprets the examinations: EEG, neuroimaging examination (CT scan of the brain or MRI scan of the brain)
- Determines the diagnosis 'epilepsy' in case of two unprovoked epileptic seizures or one seizure with epileptiform activity in the EEG in combination with deviations in the neurological status and/or pathology in the neuroimaging examinations.
- Prescribes treatment with ASDs, which is appropriate for the type of epileptic seizures/ epileptic syndrome – I monotherapy with valproates or carbamazepine, or with another ASD (oxcarbazepine, lamotrigine) if contraindications for classical ASDs exist and for special groups of patients; or issues a protocol.
- In case of frequent epileptic seizures or inability to conduct EEG and/or neuroimaging examination (e.g. a child who needs anesthesia) – refers the patient to a hospital (general acute hospital, university general acute hospital).
- After 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 adverse effects).

3. Neurology specialist/pediatric neurologist in hospital medical care

- Deals with patients with frequent and/or severe epileptic seizures, children or patients who cannot undergo EEG and neuroimaging examinations without anesthesia due to unrest, epilepsy is diagnosed after EEG, neuroimaging examinations; patients for Territorial Expert Medical Commission.
- Prescribes complete blood count, biochemistry, serum level tests of the ASD (of VPA, CBZ, PHT)
- Administers anticonvulsive treatment (i.v. or i.m.), antiedematous, when necessary.
- Prescribes treatment with an ASD, which is appropriate for the type of epileptic seizures/ epileptic syndrome – I monotherapy with Valproate or carbamazepine, or with another ASD (oxcarbazepine, lamotrigine) if contraindications for classical ASDs exist and for special groups of patients;
- Refers the patient for monitoring and follow up by a neurology specialist in outpatient care and by the general practitioner.

Follow up of patients with epilepsy

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

II. Neurology specialist/pediatric neurologist in outpatient medical care:

1. Prescribes and interprets the examinations:
 - CBC, biochemistry, serum level tests
 - 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 focal or general cerebral symptoms, head trauma.
 - In case of indications (frequent, severe epileptic seizures) or inability to conduct EEG and/or neuroimaging examination (e.g. a child who needs anesthesia) – refers the patient to a hospital (general acute hospital, university general acute hospital).
 - Refers patients to the commissions at university general acute hospital for new investigations, adjustment of ASD treatment, therapy with new ASDs in case indications exist, depending on the type of epileptic seizures and epileptic syndrome.

III. Neurology specialist/pediatric neurologist in hospital medical care- general acute hospital

1. Patients with frequent and/or severe epileptic seizures, ASD adverse reactions or organ failure, must undergo CBC, biochemistry serum level of valproate, carbamazepine and phenytoin tests as determined by the general practitioner.
2. Prescribes EEG.
3. Administers anticonvulsive treatment (i.v. or i.m.), antiedematous and antiallergic, when necessary.

4. Adjusts the administered treatment with ASDs (changes in the doses), in the combination of drugs in a polytherapy.
5. Holds consultations with other specialists, when necessary.
6. In case of patients referred by Territorial Expert Medical Commission, the type of epileptic seizures/fits (differential diagnosis with pseudo epileptic, non-epileptic paroxysmal conditions), frequency, administered ASDs (existence of serum level of ASD), EEG should be analyzed.
7. In case of status epilepticus, the treatment is conducted in an intensive care unit/sector by using intravenous forms of Diazepam, Valproate, and if needed – under narcosis with Tiopental, Midazolam or Propofol.

IV. Neurology specialist/pediatric neurologist in hospital medical care- university general acute hospital

1. Performs EEG (also under anesthesia in case of young and unrest children); video EEG, if necessary; Neuroimaging examination if the patient has not been examined or in case of progressive impairment of the 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 for experienced status epilepticus, complications, allergic reactions, ASD adverse effects and organ failure.
3. In case of status epilepticus, the treatment is conducted in an intensive care unit/sector by using intravenous forms of Diazepam, Valproate, and if needed – under narcosis with Tiopental, Midazolam or Propofol.
4. Therapy-resistant patients who are indicated for surgical treatment of epilepsy should be referred to university general acute hospitals providing conditions for continuous video-EEG monitoring, neuroimaging examinations and neuropsychological examinations for the purposes of preoperative assessment (in accordance with the enclosed protocol).
5. In case of patients referred by Territorial Expert Medical Commission, 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 should be analyzed.
6. A commission at the university general acute hospital issues an expert opinion for treatment with the new ASDs and combinations of ASDs based on the type of epilepsy, seizure frequency, preceding therapy, age, adverse effects, and/or evidence of organ failure.
7. Refers the patient for monitoring and follow up by a neurology specialist in outpatient care and by the general practitioner.

Annexes

Fig. 2. Diagnostic process in patients with epileptic seizures

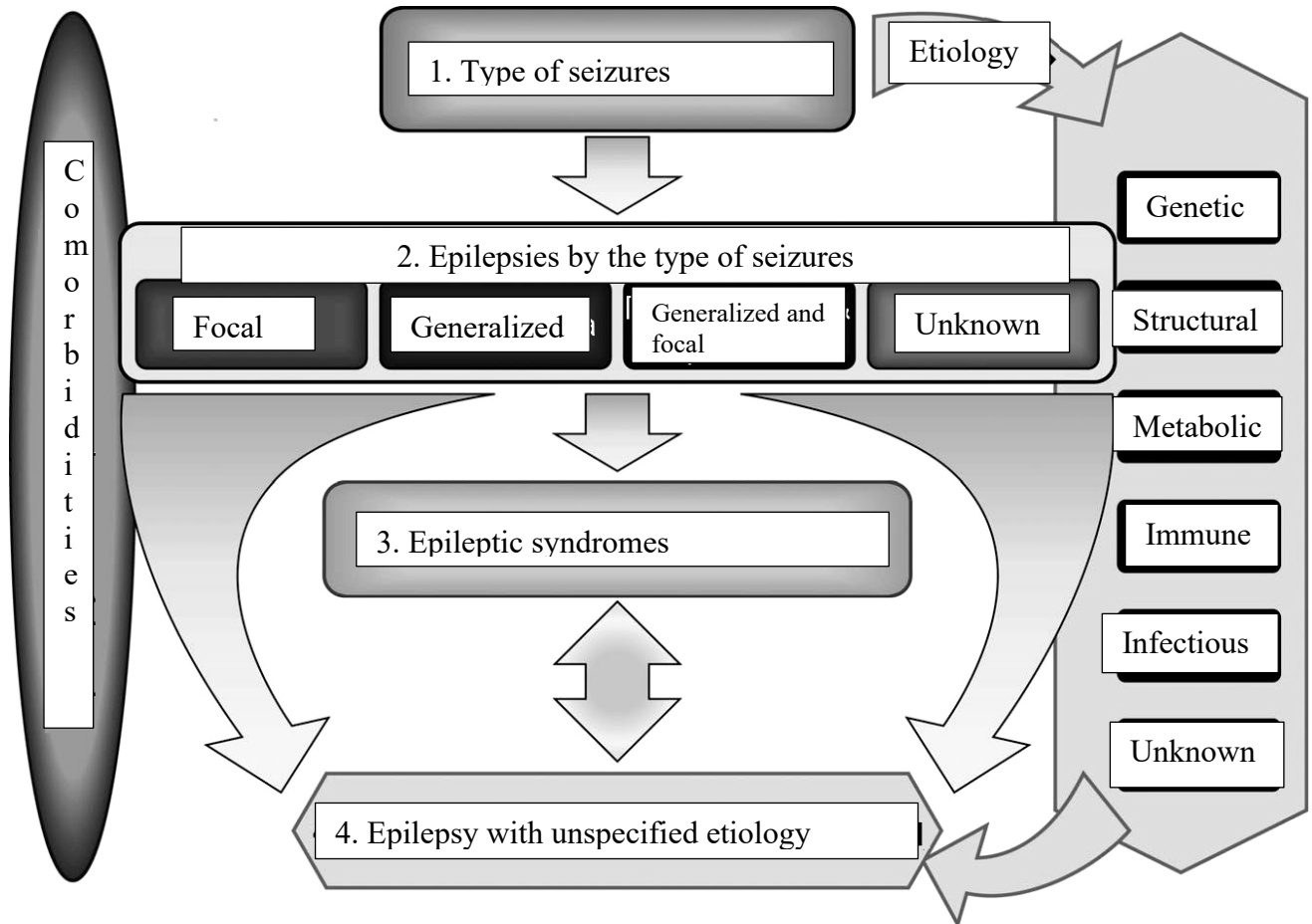
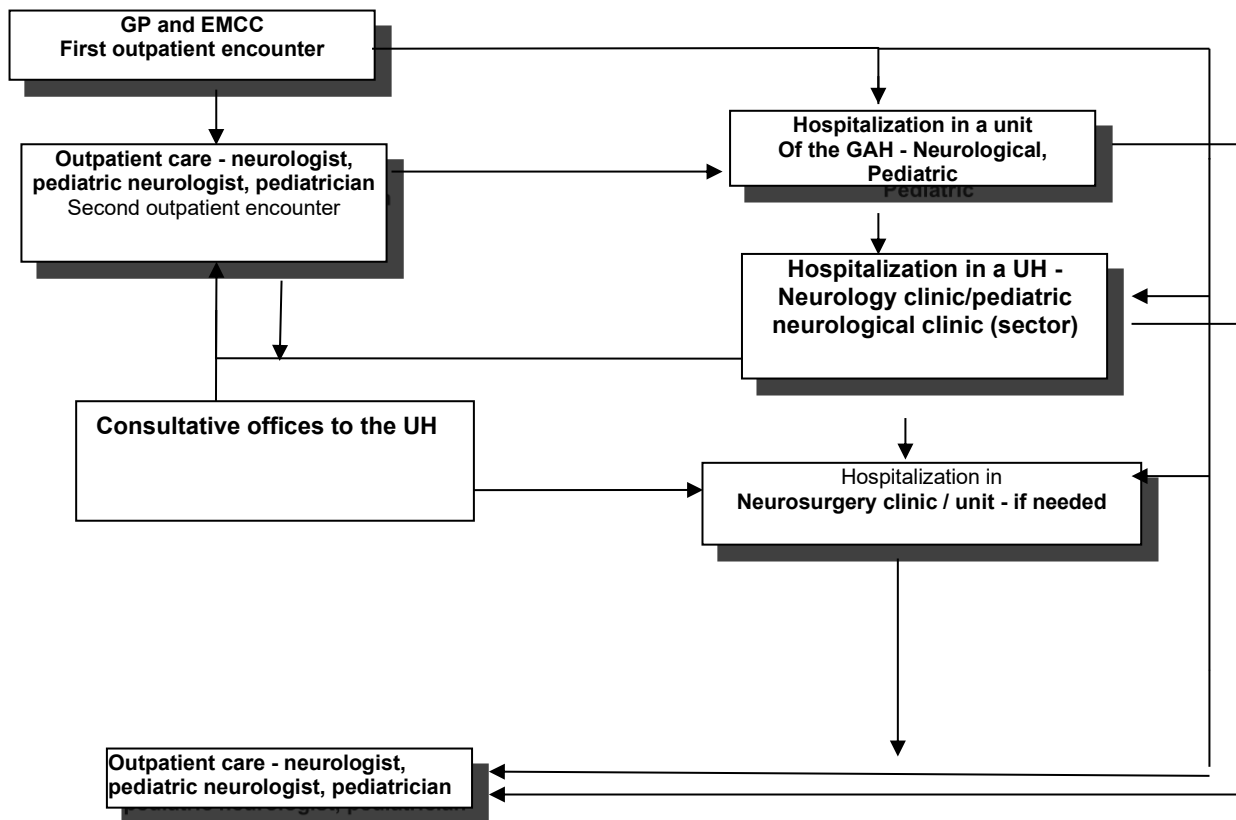


Fig. 3. Patient's roadmap



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

Fig. 4. Algorithm for diagnosis and follow-up of patients with epilepsy

