# Antiepileptics

**Epilepsy** is a common neurological disease with a variety of manifestations. The prevalence is 8-9 cases per 1000 population . Seizures are a characteristic manifestation of the disease. Seizures are divided according to the onset of the attack into:

- **focal** (seizure occurs in a localized lesion in the brain), may occur with or without impaired consciousness, may occur with motor manifestations (eg automatisms, clonic manifestations) or with other manifestations (behavioral, cognitive, emotional manifestations),
- **generalized** (seizure occurs suddenly throughout the brain), always occurs with impaired consciousness and may be accompanied by motor manifestations, or it may be an absence - a generalized seizure without motor manifestations,
- **with an unknown beginning**.

According to the type of seizures that the patient suffers from, we distinguish the **type of epilepsy** - focal, generalized, combined focal and generalized, of unknown type.

**The etiology** of epilepsy can be different - structural (after stroke, trauma), genetic, infectious, metabolic (eg in porphyria), autoimmune or unknown.

The disease is accompanied by a number of **comorbidities** - learning disorders, intellect, autism spectrum disorders, depression, movement disorders, sleep, GIT.[1]

*See the Epilepsy page for more information .*

*See the Epileptic Seizure Classification page for more information .*

**Antiepileptics** are drugs that suppress the symptoms of the disease.

## Mechanism of action

**Antiepileptics** suppress neuronal excitability. It targets a variety of receptors - **sodium** , **calcium** or **potassium** channels, **GABAergic** (inhibitory) or **glutamate** (excitatory) receptors or may bind to **synaptic proteins** . The mechanism of action of many antiepileptic drugs has not been elucidated in detail.

**Narrow-spectrum antiepileptics** affect only one of the above structures:

- Na + channels - carbamazepine, eslicarbamazepine acetate, phenytoin, lacosamide,
- Ca 2+ channels - etosuximide, gabapentin, pregabalin,
- GABA - clobazam, clonazepam, phenobarbital, primidone, tiagabine, vigabatrin,
- Glutamate - perampanel,
- Binding to synaptic proteins - levetiracetam, brivaracetam.

**Broad-spectrum antiepileptics** affect more or most of the possible target structures (valproate, lamotrigine, topiramate, phlebamate, zonisamide).

## Treatment of epilepsy

### First aid for epileptic seizures

During an ongoing epileptic seizure, we **prevent injuries** - we dangerously remove objects, support the head, and loosen clothing around the neck. We do not prevent motor manifestations of the attack and we wait for the attack to disappear, it should disappear spontaneously (motor manifestations within 5 minutes, other manifestations within 10 minutes). If the patient does not regain consciousness after the attack, we place him in a stabilized position.

In some cases, it is necessary to arrange transport to the hospital, in particular:

- if it is the first seizure or cumulation of seizures,
- if disorientation persists,
- if there is an injury that requires treatment,
- in the case of *Status epilepticus.*

### Epileptic status

If the epileptic seizure does not subside within 5 minutes in the case of motor manifestations, or within 10 minutes in the case of a seizure without motor manifestations, or if another seizure occurs without the patient becoming aware, *Status epilepticus* occurs . He always requires the earliest possible medical care. The goals of treatment are to ensure vital functions, stop the seizure, clarify its etiology and prevent recurrence - follow-up care.

For the treatment of *Status epilepticus* we administer drugs **intravenously** :

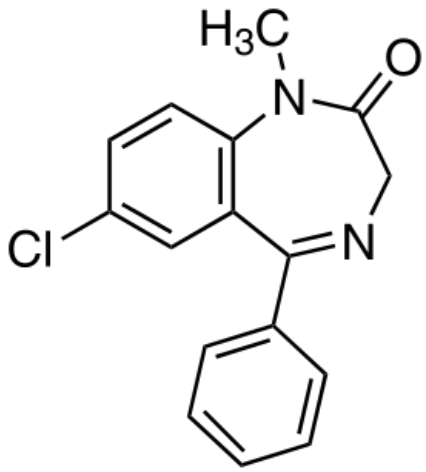
- benzodiazepines - diazepam or the more effective midazolam
- antiepileptics - phenytoin, valproate, levetiracetam, phenobarbital, lacosamide ,
- in case of thiopental ineffectiveness, propofol .

## Long-term oral treatment of epilepsy

**The goal of treatment** is to achieve seizure compensation without unacceptable side effects and to ensure the patient's optimal quality of life . In general, most patients respond well to treatment.

Treatment **is initiated with monotherapy** , the dose is gradually increased until there is a significant reduction / disappearance of seizures, until the maximum doses or signs of drug toxicity are reached. If monotherapy is ineffective, the same procedure is repeated with another drug. Only after another treatment failure (less than 10%) is the combination of more antiepileptics used .

The first seizure is usually not a reason to start treatment. Complete treatment of biochemistry and KO should be analyzed prior to treatment. The choice of antiepileptic drugs is determined by the type of seizure, more precisely by epileptic syndrome .



Diazepam Structure

### Focal seizures

1. First-line monotherapy - levetiracetam, lamotrigine.
2. Second choice monotherapy - carbamazepine, eslicacrbamazepine acetate, lacosamide, zonisamide, topiramate, valproate.
3. Adjunctive therapy - brivaracetam, clobazam, gabapentin, pregabalin.

### Generalized seizures with tonic-clonic seizures

1. First-line monotherapy - levetiracetam, lamotrigine.
2. Second-line monotherapy - topiramate, valproate.
3. Add-on therapy - levetiracetam, pregabalin, zonisamide.

### Absence

1. First choice monotherapy - etosuximide, lamotrigine, valproate.
2. Second-line monotherapy - levetiracetam, topiramate.
3. Add-on therapy - zonisamide.

### Myoclinical seizures

1. First-line monotherapy - levetiracetam, valproate.
2. Second choice monotherapy - lamotrigine.
3. Add-on therapy - benzodiazepines, levetiracetam, topiramate, zonisamide.

The control of the use of the drug is its level in the serum, which also allows individual determination of the dose.

### Treatment during pregnancy

Epilepsy is by no means a contraindication to pregnancy, but a serious side effect of some antiepileptic drugs is teratogenicity . Phenytoin, carbamazepine, valproate and phenobarbital are proven teratogens. We do not use these drugs in women of productive age unless necessary. If necessary, an appropriate method of contraception should be provided .

For women planning a pregnancy (ideally all of working age), **lamotrigine** or gabapentin is the ideal treatment option for **monotherapy** .

### Discontinuation of treatment

We consider the end of treatment at the earliest after 3 years without seizure in EEG without specific EP graphoelements, we slowly decrease with the dose (risk of rebound phenomenon!).

## Surgical treatment

**Drug-resistant patients** - compliant patients in whom two adequately selected antiepileptic drugs in monotherapy or combination failed. These patients may be indicated for surgical treatment .

*See the Surgical Treatment for Epilepsy page for more information .*

# Distribution of antiepileptic drugs by generations

The division of antiepileptic drugs into generations does not take into account either the chemical structure or the mechanism of action, but only the year of implementation. The traditional division of antiepileptic drugs into generations looks like this:

1. Generations (roughly interwar period) - phenobarbital, phenythion, ethosuximide.
2. Generations (roughly 50s to 80s) - carbamazepine, valproate and benzodiazepines .
3. Generations (drugs registered from the 90s to the present - new antiepileptics) - especially lamotrigine, levetiracetam, topiramate, lacosamide, zonisamide, gabapentin, pregabalin and others.

Since most of the substances used today fall into the third generation, we may now encounter an alternative division that combines the first and second generations and, conversely, divides substances registered since the 1990s into two generations:

1. Generation - phenobarbital, phenytoin, ethosuximide, carbamazepine, valproate and benzodiazepines.
2. Generation - phlebamate, gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, pregabalin and zonisamide.
3. Generations - lacosamide, eslicarbamazepine acetate, rufinamide, brivaracetam, perampanel, vigabatrin and clobazam.

# Overview of antiepileptics

## Broad-spectrum antiepileptics

Broad-acting substances useful in a number of indications, usually the drugs of choice.

**Valproate**
*Mechanism of action:* broad-spectrum antiepileptic drug, blocks Na + and Ca 2 and also potentiates GABA, *Indications for* all types of seizures, drug of choice for generalized seizures, *Side effects:* quite significant - tremor, weight gain, hepatotoxicity, thrombocytopenia, teratogenicity!

**Lamotrigine**
*Mechanism of action:* acts on both Na + and Ca 2+ and suppresses the action of excitatory amino acids, *Indications:* focal and generalized seizures, drug of choice in women of childbearing age - can be used in pregnancy, in psychiatry as a "mood stabilizer" *Side effects:* redness, rash, toxic epidermal necrolysis - occurs with rapid onset of high doses, somnolence, ataxia, diploidy.

**Topiramate**
*Mechanism of action:* very broad-spectrum entiepiletic, acts on Na + and Ca 2+ channels, blocks AMPA glutamate receptors, potentiates GABA, weakly inhibits carbonic anhydrase, *Indications:* very broad - focal and generalized seizures in children and adults, migraine *Side effects:* somnolence, disorders concentrations, cognition, paraesthesia - worsen with rapid dose titration

**Zonisamide**
*Mechanism of action:* blockade of Na + and Ca 2+ channels inhibition of acrboanhydrase, modulation of dopaminergic and seroronergic systems, *Indications:* therapy of focal seizures, *Adverse effects:* somnolence, ataxia, but also severe skin reactions - titrate the dose slowly

**Levetiracetam**
*Mechanism of action:* not completely known, binds to synaptic vesicular protein SV2A, *Indications:* focal seizures, generalized tonic-clonic seizures, myoclonic seizures, *Side effects:* rarely aggression, practically no drug interactions [2][3]

**Clonazepam**
*Mechanism of action:* GABA potentiation, *Indications:* iv in status epilepticus, focal and generalized seizures - reserved for resistance to other antiepileptics.

## Narrow-spectrum antiepileptics

Narrow-acting substances reserved for specific epileptic syndromes, such as adjunctive therapy, or new substances still waiting to be extended.

**Phenobarbital**
*Mechanism of action:* acts on GABA A receptors, *Indications:* due to side effects very limited today, acts on focal and generalized tonic-clonic seizures, wide application in veterinary practice or in developing countries, *Side effects:* depression, depression, behavioral changes

**Primidon**
prodrug - in the liver is metabolized to phenobarbital, *Mechanism of action:* GABA potentiation, *Indications:* focal and generalized tonic-clonic seizures - only as adjunctive therapy, *Side effects:* depression, ataxia

**Phenytoin**
*Mechanism of action:* blockade of Na + channels, *Indications:* focal epilepsy (second-line drug), worsens generalized forms, *Side effects:* relatively numerous - nystagmus, ataxia

**Ethosuximide**
*Mechanism of action:* inhibition of T-type Ca 2 channels, *Indications:* absence, *Side effects:* significant, especially on the GIT [2]

**Carbamazepine**
*Mechanism of action: Na* + channel blockade , *Indications:* drug of choice for focal seizures, *Metabolism:* is a substrate and a strong inducer of CYP 3A4, reduces the effect of many drugs (hormonal contraceptives !, warfarin !, other antiepileptics, doxycycline, theophylline, corticoids, tricyclic antidepressants) ), *Side effects:* somnolence, diplopia, vertigo [2]

**Klobazam**
*Mechanism of action:* potentiation of GABA (benzidiazepine derivative), *Indications:* focal and generalized seizures in drug-resistant epilepsy[2]

**Flebamate**
*Mechanism of action:* influence of Na + and Ca 2+ channel and blockade of NMDA receptor for glutamate, *Indications:* in the Czech Republic only Lennox-Gastaut syndrome due to possible side effects, *Side effects:* aplastic anemia, hepatic failure[2][3]

**Gabapentin**
*Mechanism of action:* Ca 2+ channel effect, increased GABA synthesis *Indications:* peripheral neuropathy, focal epilepsy, *Side effects:* weight gain[3]

**Pregabalin**
*Mechanism of action:* Ca 2+ channel effects, *Indications:* peripheral neuropathy, anxiety disorders adjunctive therapy in focal attacks *Adverse effects:* somnolence, dizziness, weight gain [2][3]

**Tiagabine**
*Mechanism of action:* inhibition of GABA reuptake, *Indications:* focal seizures (generalized worsens), *Side effects:* somnolence, dizziness, anxiety, depression, *Interactions:* substrate P450 - inducers accelerate metabolism [2][3]

**Vigabatrin**
*Mechanism of action:* increased GABA concentration in the synaptic cleft, *Indications:* West's syndrome (infantile spasms)[2][3]

**Lacosamide**
*Mechanism of action: Na* + channel blockade , *Indications:* adjunctive therapy in focal attacks, *Side effects:* dizziness, headache, nausea, blurred vision - not suitable for patients at risk of suicide [3]

**Rufinamide**
*Mechanism of action:* not elucidated, probably interactions in Na + channels, *Indications:* Lennox-Gastaut syndrome[2][3]

**Eslicabamazepine acetate**
*Mechanism of action: Na* + channel blockade , *Indications:* focal seizures, *Side effects:* dizziness, somnolence - partial (1 of 10), *Interaction:* virtually none (although structurally similar to carbamazepine) [3]

**Perampanel**
*Mechanism of action:* glutamate AMPA receptor antagonist, *Indications:* adjunctive therapy in focal seizures, *Adverse effects:* dizziness, somnolence [3]

**Brivaracetam**
*Mechanism of action:* binding to the synaptic vesicular protein SV2A, *Indications:* adjunctive therapy in focal seizures [3]

# Links

## References


1. KUBA, Robert. Antiepileptics and their clinical use in epileptology. *Practical pharmacy* [online] . 2010, vol. 10, vol. 6, no. 2, pp. 62-66, also available from < https://www.solen.cz/artkey/lek-201002-0002_Antiepileptika_a_jejich_klinicke_pouziti_v_epileptologii.php >. ISSN 1803-5329.
2. ↑ MARUSIČ, Petr, Hana OŠLEJŠKOVÁ and Milan BRÁZDIL. Classification of the epileptic seizures and classification of the epilepsies ILAE 2017. *Neurologie pro praxi.* 2018, year. 1, vol 19, pp. 32-36, ISSN 1213-1814. DOI: 10.36290 / neu.2018.075 .
3. ↑Jump up to:a b c d e f g h i *Incomplete citation of the publication.* MARUSIC, Petr, et al. *A set of minimum diagnostic and therapeutic standards for patients with epilepsy* [online] . 2017. Also available from <www.epistop.cz>. ISBN 978-80-906982-0-8 .

4. ↑ STRZELCZYK, Adam, Johann Philipp ZÖLLNER and Laurent M. WILLEMS. Lacosamide in status epilepticus: Systematic review of current evidence. *Epilepsy.* 2017, year. 6, vol 58, pp. 933-950, ISSN 0013-9580. DOI: 10.1111 / epi.13716 .
5. ↑Jump up to:a b c d e SEIDL, Zdeněk and Jiří OBENBERGER. *Neurology for study and practice.* 1st edition. Prague: Grada Publishing, 2004. ISBN 80-247-0623-7 .
6. ↑Jump up to:a b c d e f g h i j k l m n o p SYNEK, Stanislav. *News in neurology* . Paper presented at the conference Pharmacology and Pharmacotherapy of Selected Diseases. Prague. 2019
7. ↑Jump up to:a b LAPENNA, Paul and Laura M. TORMOEHLEN. The Pharmacology and Toxicology of Third-Generation Anticonvulsant Drugs. *Journal of Medical Toxicology.* 2017, year. 4, vol 13, pp. 329-342, ISSN 1556-9039. DOI: 10.1007 / s13181-017-0626-4 .

## Related articles

- Epilepsy
- Surgical treatment of epilepsy

1.
2.
3.