Pharmacology

Antiepileptic drugs

Marta Jóźwiak-Bębenista
Department of Pharmacology
Medical University of Lodz
martia1@tlen.pl
Epilepsy

- one of the most common neurologic disorders
- one of the oldest conditions known to mankind
- People with epilepsy are just like everybody else, except they sometimes have seizures.
- More men than women have epilepsy.
Epilepsy is a neurological disorder that affects people in every country throughout the world. About 7.2 million people will experience at least one seizure during their lifetime. In the US, more than 2.3 million people are affected by seizures. In Poland approximately 400,000 people suffer from epilepsy. Epilepsy can develop at any age. New cases of epilepsy are most common among children, especially during the first year of life. The rate of new cases gradually declines until about age 10, and then becomes stable. After age 55 or 60, the rate starts to increase, as people develop strokes, brain tumors or AD.
Some people can experience a seizure and not have epilepsy.

A single seizure does not mean that the person has epilepsy.

Types of seizures not classified as epilepsy:

→ Febrile convulsions
→ Seizures caused by an imbalance of body fluids or chemicals or by alcohol or drug withdrawal.
Epilepsy is characterized by unprovoked, recurring seizures that disrupt the nervous system and can cause mental and physical dysfunction.

It is usually diagnosed after a person has had at least two seizures that were not caused by some known medical condition like alcohol withdrawal or extremely low blood sugar.

Epileptic seizures vary in severity and frequency, some people may experience no more than 2-3 seizures during their entire lifetime, others will have several seizures in one day.
First aid for convulsive epileptic seizures

- Stay calm.
- Note the time.
- Prevent others from crowding round.
- Put something soft under the person’s head - like a jacket to prevent injury.
- Only move if they are in a dangerous place, such as in the road or at the top of stairs. Move things away from them if there is a risk of injury.

- Do not attempt to restrain the convulsive movements. Allow the seizure to take its course.
- Do not put anything in the person’s mouth. There is no danger of swallowing the tongue and teeth can easily be broken.
Seizures

- The result of sudden, usually brief, excessive electrical discharges in neurons, causing a temporary disruption in the normal message passing between brain cells.
- The abnormal electrical activity in the brain causes an involuntary change in body movement or function, sensation, awareness, or behavior.

- This brief electrical surge can happen in just a small area of the brain, or it can affect the whole brain.
Seizures

The symptoms of each seizure type depend on the area of the brain in which they are active and on the extent to which the electrical activity spreads to other neurons in the brain.

- In parietal or occipital cortex
  - Sensory experience: visual, auditory or olfactory hallucinations

- In the motor cortex
  - Convulsions
1. Partial:
   a) simple partial
   b) complex partial

2. Generalized:
   a) generalized tonic-clonic (grand mal)
   b) absence (petit mal)
   c) myclonic seizures
   d) atonic seizures
   e) status epilepticus
   f) febrile seizures
Partial seizures

arise from an electric discharge of one localized area of the brain

- **simple partial**
  The patient doesn`t lose consciousness and exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain, experiencing excessive electrical discharges.
  - lasting 60-90 seconds
  - may occur at any age

- **complex partial**
  The patient loses consciousness and exhibits complex sensory hallucinations and mental distortion. Motor dysfunction includes chewing movements (lip macking, swallowing) diarrhea, urination.
  - 30-120 seconds
  - before 20 years of age.
Generalized seizures

begin in a localized area of the brain, but then rapidly spread, producing abnormal electrical discharge throughout both hemispheres of the brain.

Grand mal
- the most dramatic of all epileptic seizures
- an initial contraction of the muscles (*tonic phase*) (tongue biting, urinary incontinence, absence of breathing)
- followed by rhythmic muscle contractions (*clonic phase*)
- Loss of consciousness
- duration usually 3 min.

Petit mal
- characterized by sudden onset and abrupt cessation
- an interruption to consciousness where the person experiencing the seizure seems to become vacant and unresponsive for a short period of time.
- Duration less than 10 seconds.
- begin in childhood
Generalized seizures

Myoclonic seizures
- sporadic muscle contraction
- jerky movements of muscles or muscle groups
- rare, occur at any age
- often a result of permanent neurologic damage acquired as result of hypoxia, uremia, encephalitis or drug poisoning.

Atonic seizures
- loss of muscle tone, causing the person to fall to the ground.
- called 'drop attacks' but should be distinguished from similar looking attacks that may occur in narcolepsy or cataplexy.
Generalized seizures

**Status epilepticus**
- Continuous seizure activity with no recovery between successive tonic-clonic seizures.
- Seizures are rapidly recurrent.

- This is a life threatening condition and emergency medical assistance should be called immediately if this is suspected.

- Seizures that go on for more than 20 to 30 min. during which the person does not wake up can cause brain damage.

- Treatment with antiepileptic medications needs to be started immediately for any seizure lasting more than 5 minutes.

- Medication used to end the seizure is given through an IV - Diazepam (rectally, muscle)
The seizures in epilepsy may be related to a brain injury or a family tendency, but most of the time the cause is unknown.

- **Idiopathic epilepsy** or primary epilepsy
  - is thought to be caused by genetic factors
  - Patients are treated chronically with antiepileptic drugs, often for life.

- **Symptomatic epilepsy** or secondary epilepsy
  - is caused by widespread brain damage: injury during birth; brain infections—meningitis, encephalitis; strokes, tumors, cysts trauma, "sclerosis" of brain tissue
  - damage resulting from high fever, stroke, toxicity, alteration in blood gases, pH, electrolytes or glucose availability.
What factors trigger epilepsy?

- Inadequate sleep.
- Food allergies.
- Alcohol and smoking - alcohol and smoking should be avoided. Excess alcohol can trigger a seizure even in people without epilepsy.
- Flashing or bright lights - watching TV or playing video games can trigger a seizure.
- Stress
- Fever - a high temperature (fever) can bring on a seizure in young children if they are ill. This is less likely in adults.
- Certain medications
- Hyperventilation - breathing too fast or too deeply
- Hormones - many woman report that their seizures are linked to their menstrual cycle - though no one really knows why.
The hypothesis of epileptic seizures

A seizure reflects an imbalance between excitatory and inhibitory activity in the brain, with an increment of excitation over inhibition.

- The deficit of inhibitory neurotransmitters - GABA
- Antiepiletics can enhance the GABA system by:
  - blocking presynaptic GABA reuptake - Tiagabine
  - inhibiting the metabolism of GABA by blocking GABA transaminase - Vigabatrin
  - increasing the synthesis of GABA - Valproate
  - direct binding to GABA-A receptors - benzodiazepine, barbiturates
The excess of stimulating amino acids like glutamate acid, which activate receptors NMDA

Some antiepileptics drugs can reduce the effectiveness of natural excitatory neurotransmitters, such as glutamate by:

- block glutamate receptors (Topiramate)
The hypothesis of epileptic seizures

- **Sodium channels**
The firing of an action potential by an axon is accomplished through Na\(^+\) channels. The blockade of Na\(^+\) channels of the axons causes stabilization of the neuronal membranes, limits the development of maximal seizure activity, and reduces the spread of seizures.

- **Calcium channels**
Petit mal seizures are caused by activation of calcium channels type T. AEDs that inhibit these T- calcium channels are particularly useful for controlling absence seizures.
The main groups of antiepileptics include sodium channel blockers, calcium current inhibitors, gamma-aminobutyric acid (GABA) enhancers, glutamate blockers. The AEDs can be grouped according to their main mechanism of action, although many of them have several actions and others have unknown mechanisms of action.

Drug Withdrawal

When anti-epileptics are stopped abruptly, seizures may result.
Treatment of epilepsy

- **Appropriate drug treatment depends on:**
  - the classification of the epilepsy
  - the nature of the seizure,
  - the electroencephalographic (EEG) pattern.

- **The choice of drug depends on:**
  - The type of epilepsy! (Grand mal seizures are treated differently than petit mal, but several drugs may be equally effective and the toxicity of the agent is often a major consideration in drug selection)
  - Possible side effects.
  - Anticipation of pregnancy
  - Other medications (interactions)
Anti-epileptic drugs

- Anti-epileptic drugs are also known as "anticonvulsant", since they prevent convulsions. It's preferred to call them anti-epileptic, because, not all forms of epilepsy involve convulsions.

- Monotherapy in the treatment of epilepsy is recommended. When therapy with a single epileptic drug is ineffective, a second drug may be added.

- Antiepileptic therapy should never be terminated abruptly!
Therapeutic uses
Seizures types and drug classes

- Simple partial:
  - Carbamezepine
  - Phenytoin
  - Phenobarbital
  - Primidone
  - Gabapentin
  - Lamotrigine

- Complex partial:
  - Carbamazepine
  - Phenytoin
  - Primidone
  - Lamotrigine
  - Gabapentin

- Petit mal
  - Ethosuximide
  - Valproate

- Grand mal
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Primidone
  - Valproate

- Status epilepticus
  - Phenytoin
  - Diazepam
  - Phenobarbital
Phenytoin

- The oldest of the effective major anti-epileptic drugs
- Still one of the most potent epileptic in preventing major seizures of tonic-clonic and partial seizures.

**Mechanism of action:**
- blocks the sodium channels
- inhibits the calcium channels
- calmodulin and other secondary messenger systems
Phenytoin is one of the most commonly used first-line or adjunctive treatments for:
- partial seizures,
- tonic-clonic seizures
- status epilepticus.

It is not indicated for:
- absence seizures
- myoclonus.

highly effective and economical for the patient
tolerability of the drug is still in dispute.
Pharmacokinetics of phenytoin

- absorbed upon oral administration rather slowly in the small intestines
- oral bioavailability- approximately 95%, largely 70-95% bound to plasma protein-albumin.
- metabolized by the hepatic P-450 mixed oxidase system
- excretion is through the kidneys
- At low doses: half-life of 24 hours, as the dosage ↑ → the hepatic hydroxylation system becomes saturated → small increases in dose of phenytoin ⇒ a large ↑ plasma concentration of drug ⇒ drug-induced toxicity.

The plasma concentration of phenytoin should be monitored!
Adverse effects of phenytoin

- drowsiness and lethargy - without progressing to hypnosis
- ataxia, nystagmus
- nausea, vomiting, rash, blood dyscrasias, vit. K and folate deficiencies
- loss of libido, hormonal dysfunction
- bone marrow hypoplasia
- vit. B12 deficiency resulting in megaloblastic anemia.
- growth of hair on the face, arms and legs, especially in female patients of dark complexion
- unhealthy overgrowth of the gums
- When given during pregnancy, like other AEDs, can cause cleft palate, cleft lip, congenital heart disease, slowed growth rate, and mental deficiency in the offspring. This teratogenic effect named “Fetal hydantoin syndrome”.
- **Overdose** of drug produces symptoms similar to drunkenness, with drowsiness, unsteadiness on the feet.
Among all AEDs, phenytoin has one of the most problematic drug interaction profiles, because of:
- its highly protein-bound (>90%) nature
- its metabolism by the P-450 enzymes
- Phenytoin *induces the cyt. P450* which leads to an increase in the metabolism of other drugs, which are metabolized by enzymes of cytochrome P450.
- hepatic enzyme inducers (carbamazepine)
- hepatic enzyme inhibitors (cimetidine, sulfonamides, dicumarol)
Epileptologists, in general, try to avoid prescribing phenytoin because of the poor side-effect profile. Despite the difficult pharmacokinetics and the adverse effects, this drug is used widely. The once-a-day dosing, good efficacy, many years of experience, possibility of monitoring the plasma levels, and availability of a parenteral preparation make it suitable for use by the primary care physician.
Carbamazepine

- Mechanism of actions:
  - block sodium channels

- Pharmacokinetics:
  - CBZ is a potent inductor of hepatic cytochrome P450 isoenzyme system
  - its plasma half-life therefore decreases with chronic administration.

- The extended-release preparations, Tegretol XR are better tolerated than the immediate-release preparations.
CBZ is one of the most widely used AEDs in the world. It is highly effective for:

- all partial seizures (drug of first choice)
- generalized tonic-clonic seizures
- trigeminal neuralgia

The drug is highly effective and well tolerated. The major disadvantages of this drug are transient adverse dose-related effects when initiating therapy and occasional toxicity.
Ethosuximide

- This drug is effective in controlling one form of epilepsy only **absence seizures**

  - **Mechanism of action:**
    - block sodium channels
    - block T-type calcium channels

- It is preferred clinically because of the ease of patient tolerance, degree of seizure reduction, long half-life, and lack of drug interactions with other AEDs.
Ethosuximide

Adverse effects and toxicity:

- dizziness,
- drowsiness,
- headache,
- lethargy,
- agitation,
- anxiety,
- weight gain.

Gradual titration of the drug appears to reduce the manifestations of adverse reactions.
Benzodiazepines

Mechanism of action: agonist action at the GABA-A receptor.

- Sedative and anti-anxiety properties
- Never used as a first choice drugs
- Situations where epilepsy remains uncontrolled
  - Lorazepam - ATIVAN
  - Diazepam - VALIUM
  - Clonazepam - RIVOTRIL
  - Clorazepate - TRANXENE
Benzodiazepines

- **Lorazepam, Diazepam** - used mainly for emergency treatment of seizures because of their quick onset of action, availability of IV-intravenous forms, and strong anticonvulsant effects.

- **Diazepam** is the drug of choice in the acute treatment of status epilepticus.

- **Clonazepam** is effective in absence and myoclonic seizures, but tolerance may also develop.

- **Clorazepate** is effective in partial seizures when used in conjunction with other drugs.
Benzodiazepines

- **Adverse side effects:**
  - sedation, drowsiness
  - restlessness,
  - sleep disturbances (after a long period of administration)
  - risk of producing drug dependency.

- Their use for long-term treatment is limited because of the development of tolerance.
Barbiturates- Phenobarbital

- Very potent anticonvulsant with a broad spectrum of action
- Its use is limited because of its adverse effects.
- **Mechanism of action:**
  - Direct action on GABA-A receptors by binding to the barbiturate-binding site
  - Reduces sodium and potassium conductance and calcium influx and depresses glutamate excitability.

**Pharmacokinetics:**
- Well absorbed upon oral administration.
- Powerful inducer of the hepatic microsomal enzymes

**Therapeutic uses:**
- Drug of choice in febrile seizures in children.
- Simple partial seizures
- Tonic-clonic generalized seizures
- Status epilepticus.
Phenobarbital

- **Adverse effects:**
  - Sedation is prominent,
  - Psychomotor slowing,
  - Poor concentration-learning problems,
  - Depression,
  - Irritability,
  - Ataxia,
  - Decreased libido
- Rebound seizures can occur on discontinuance of phenobarbital.

- Cautiously in children treated for febrile seizures, because can depress cognitive performance.

- Inducer Cyt. P450 increases the metabolism of drugs.

- Not very effective for complex partial seizures, not effective in petit mal.
Conclusion

Phenobarbital still is a first-line drug for treatment of status epilepticus. However, because of its adverse-effect profile, it is a second-line agent in the treatment of partial onset and secondarily generalized tonic-clonic seizures. In developing countries, it is used widely because of its low cost.
Barbiturates - Primidone

**Therapeutic uses:**
- tonic-clonic
- simple partial seizures
- complex partial seizures (PEMA)

Primidone is ineffective in absence seizures!

Primidone exerts the same side effects as phenobarbital

- prolong action of the parent drug

Primidone

phenobarbital

phenylmethylmalonamide (PEMA)
Valproic acid - Valproate

- **Therapeutic uses:**
  - myoclonic seizures
  - tonic-clonic seizures
  - absence seizures

- **Pharmacokinetics:**
  - rapidly absorbed upon oral administration.
  - 85-95% bound to plasma proteins.
  - metabolized by the Cyt. P450 system, but it does not induce or inhibit this system.
  - hepatotoxic

- **Mechanism of actions:**
  - effects on GAD enzyme
  - block Na+ channels

![Diagram of GAD enzyme and glutamate decarboxylation](image)
The newest antiepileptics

- suppress seizures by:
  1. increasing inhibition (through ↑GABA)
  2. reducing the effectiveness of natural excitatory neurotransmitters, (↓glutamate)

- less severe cognitive effects than older drugs

  Tiagabine (Gabilitrill)
  Lamotrigine (Lamictal)
  Topiramate (Topamax)
  Gabapentin (Neurontin)
Mechanism of actions:
inhibits neuronal reuptake of GABA

Therapeutic uses:
- partial seizures
- secondarily generalized seizures in refractory patients

Adverse effects:
dizziness,
- asthenia,
- nervousness,
- tremor,
- depressed mood,
- emotional lability.

No changes in biochemical or hematological parameters
Lamotrigine

- **Mechanism of actions:**
  - block Na+ channels
  - inhibit release of glutamate

- **Therapeutic uses:** It is effective in all kind of seizures:
  - partial seizures
  - generalized tonic-clonic seizures.

- **Pharmacokinetics:**
  - well absorbed upon oral administration
  - bioavailability close to 100%
  - protein binding is 55%
  - no effects on hepatic Cyt.P450 enzymes

- **Adverse effects:**
  - few CNS side effects
  - allergic reactions (skin rashes)
Conclusion:

Lamotrigine is a very effective and well-tolerated drug. **Combination therapy** with valproate enhances the antiepileptic effect; however, it also increases the chances of developing allergic skin reactions. Very slow titration is important for better tolerability.

The excellent side-effect profile and lack of significant CNS toxicity make this drug one of the preferred choices in treating elderly patients. The reported low incidence of congenital malformations when exposed to pregnant patients makes this drug one of the preferred treatments during pregnancy.
Topiramate

- derived from D-fructose
- very potent anticonvulsant

Mechanism of action:
- blocks Na+ channels
- increases GABA activity at GABA receptors,
- inhibits the AMPA subtype glutamate receptor,
- weak inhibitor of carbonic anhydrase.

Therapeutic uses:
reduces the number of partial seizures in refractory patients

Side effects:
- ataxia,
- impairment of concentration,
- confusion,
- dizziness,
- somnolence,
- nervousness,
- gastrointestinal disturbances (nausea, weight loss).

Teratogenic.

reduces ethyl estradiol levels and may inactivate the low-dose contraceptive pill.
Conclusion
Most physicians agree that topiramate is a highly effective antiepileptic. The adverse cognitive effects occur more frequently at higher doses and with a rapid titration rate. Some patients with epilepsy may benefit from this drug because of its weight-loss-inducing effect. Also, it may effective as a prophylactic agent in patients with migraine headaches.
Gabapentin

- Structure similar to that of GABA

**Mechanism of action:**
- ↑intracellular concentration of GABA
- mechanism unknown
- no action on the GABA receptor.

**Therapeutic uses:**
(like lamotrigine)

**Pharmacokinetics:**
- not bound to plasma proteins
- not metabolized
- not induce hepatic enzymes.
- excreted in an unchanged form

**Adverse effects:**
- well tolerated
- adverse effects: mild CNS effects
Vigabatrin

- close structural analog of GABA

**Mechanism of actions:**
- inhibits the enzyme
  GABA transaminase (GABA-T)
  \[\downarrow\]
  \[\uparrow\] GABA

- binds irreversibly to the active site of GABA-T. (GABA-T requires three days to be resynthesized)

**Adverse effects:**
- drowsiness
- dizziness.
- minimal drug interactions

Vigabatrin is a very potent drug. The drug was licensed worldwide, except in the United States.

**Therapeutic uses:**
reduces the number of partial seizures in refractory patients
To work effectively, blood levels of anti-epileptic medications must be maintained within a certain range. If the levels rise too high toxic symptoms (drowsiness, unsteadiness on the feet) may appear. If levels fall too low, epileptic control will be inadequate. Checking blood levels is a vital part of treatment.
Therapeutic uses
Seizures types and drug classes

- Simple partial:
  - Carbamezepine
  - Phenytoin
  - Phenobarbital
  - Primidone
  - Gabapentin
  - Lamotrigine

- Complex partial:
  - Carbamazepine
  - Phenytoin
  - Primidone
  - Gabapentin

- Petit mal:
  - Ethosuximide
  - Valproate

- Grand mal:
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Primidone
  - Valproate

- Status epilepticus:
  - Phenytoin
  - Diazepam
  - Phenobarbital