Lecture 3
Antiseizure Drugs (antiepileptic drugs)

1. Antiseizure Drugs (antiepileptic drugs)
   I. Barbiturates: Phenobarbital and congeners (Primidone)
   I.2. Hidantoines: Phenytoin, Fosphenytoin, Mephenytoin, Ethotoin, Phenacemide
   I.3. Tricyclic compounds: Carbamazepine
   I.4. Succinimides: Ethosuximide, Phensuximide, Methsuximide
   I.5. Carboxilic acids: Valproic Acid, Sodium valproate
   I.6. Oxazolidinediones: Trimethadione, Paramethadione, Dimethadione
   I.7. Benzodiazepines used as anticonvulsant therapy: Diazepam, Lorazepam, Clonazepam, Nitrazepam, Clorazepate, Clobazam
   I.8. Bromides
   I.9. Carbonic anhydrase inhibitors: Acetazolamide

Epilepsy is a disease characterized by abnormal and excessive electrical activity in the central nervous system, which result in symptoms of limited duration (involuntary contractions of skeletal muscles, loss of consciousness, abnormal movements, behavioral manifestations, distorted perceptions).

Antiseizure Drugs (antiepileptic drugs) are pharmacologically active substances indicated in the treatment of epilepsy and of seizures of various etiologies (intoxication, metabolic disorders, injuries of the central nervous system etc).

Classification of epileptic seizures:
- Partial seizures (originate in localized area of cortex)
  - Simple partial seizures is associated with motor, sensory, autonomic or psychic symptoms; there is preservation of consciousness.
    - Particular form: Jacksonian seizure is characterized by motor seizures which begin in a restricted region such as fingers and gradually progress to a larger portion of the extremity.
  - Complex partial seizures is associated with automatism (purposeless movements such as lip smacking, chewing, hand wringing, aimless walking etc) associated with impairment of consciousness.
  - Simple partial seizures with secondarily generalized tonic-clonic seizures is a particular form characterized by symptoms of partial epilepsy (simple or complex), followed by symptoms of grand mal epilepsy (tonic-clonic seizures).
- Generalized seizures (involve diffuse regions of the brain in both hemispheres)
  - Tonic-clonic seizures (grand mal epilepsy) is characterized by sudden loss of consciousness and loss of postural control, muscular contractions (evolute in two phases: initial is a tonic phase characterized by continuous contraction with teeth-clenching and rigidity in extension, followed by clonic phase characterized by rapid rhythmic muscular contraction and relaxation). Tongue-biting and incontinence may occur during the seizure. Recovery of consciousness is typically gradual over many minutes to hours. Headache and confusion are common postictal phenomena.
  - Absence seizures (petit mal epilepsy) is characterized by abrupt onset of impairment of consciousness, with staring and cessation of ongoing activities, but without loss of postural control, typically lasting <30 seconds.
  - Myoclonic seizures are characterized by brief (shock-like) contractions lasting for few seconds/minutes and may be restricted to part of one extremity or may be generalized.
  - Febrile seizures are characterized by seizures induced by high fever between the age of 6 months and 3-4(5) years.
  - Status epilepticus is life-threatening disorder characterized by continuous seizures (>15–30 min) or repetitive, with impaired consciousness (without recovery of full consciousness between episodes).
Particular forms of epilepsy:

- **Infantile spasms (West syndrome)** is a severe form of epilepsy characterized by sudden muscular contractions followed by stiffening, developmental regression (mental retardation) and a specific pattern on electroencephalography testing called hypsarrhythmia (chaotic brain waves).

- **Lennox-Gastaut syndrome** is a severe form of epilepsy characterized by mental retardation or regression and multiple types of seizures (tonic-clonic, tonic, atonic, myoclonic, and atypical absence seizures).

**History of Antiepileptic Drug Therapy**

- 1857 - Bromides
- 1912 - Phenobarbitone
- 1937 - Phenytoin
- 1944 - Trimethadione
- 1954 - Primidone
- 1960 - Ethosuximide
- 1974 – Carbamazepine, Oxcarbazepine
- 1975 - Clonazepam
- 1978 - Valproate
- 1993 - Felbamate, Gabapentin
- 1995 – Lamotrigine, Levetiracetam
- 1997 - Topiramate, Tiagabine

The objectives of antiseizure therapy:

- to reduce the frequency of attacks;
- to normalize EEG between seizures of epilepsy;
- social integration between seizures of epilepsy.

All antiseizure drugs have a **narrow therapeutic index** (with the exception of benzodiazepines) and duration of treatment is all life (it is necessary periodic clinical, biochemical and haematological evaluation).

Replacement with an antiseizure drug another antiseizure drug is progressively: the dose of the former antiseizure drug is progressively reduced and the new dose of antiseizure drug is gradually increased until complete replacement.

Abrupt discontinuation of the administration of antiseizure drug determine withdrawal syndrome called status epilepticus.

The treatment of status epilepticus (regardless of the origin of epilepsy) is with benzodiazepines (particularly Clonazepam or Diazepam iv).

Common side effects of antiseizure drugs (antiepileptic drugs) include somnolence, fatigue, ataxia, dizziness, gastrointestinal upset. Patients should be counseled that these effects could impair driving and the ability to safely operate complex machinery. Use of alcohol can magnify these effects.

1. Barbiturates and related substances

   **Classification:**
   - Phenobarbital:
   - related substances: Primidone.

   **Particularities:**
   - Primidone is a prodrug, which is metabolised to Phenobarbital.
   - The anticonvulsant doses of barbiturates do not produce excessive sedation.
   - Barbiturates do not determine tolerance to anticonvulsant effect.
   - Primidone is indicated only as anticonvulsant drug.

   Mechanisms of action, pharmacodynamic effects, pharmacokinetics, indications, contraindications, side effects → see in Chapter "anxiolytic-sedative-hypnotics".
2. Hydantoins

Classification
- Phenytoin
- Phosphenytoine
- structural analogues: Mephenytoin, Ethotoin
  Phenacemide (has been withdrawn from the market)

Phenytoin (diphenylhydantoin) is the oldest non-sedating anticonvulsant, introduced in therapy in 1938.

Mechanisms of action:
- block the voltage-gated sodium channels (selectively bind to the channel in the inactive state and reduce the ability of the channel to recover from inactivation);
- inhibition of transmembrane calcium flux;
- inhibition of bone marrow post-tetanic potential;
- stimulation of Na + / K + - ATP - ase glial cell membrane;
- inhibition of release of noradrenaline and serotonin;
- stimulation of dopamine uptake and inhibition of MAO activity;
- stimulation of acetylcholine cleavage;
- antagonise the effects of glutamate;
- inhibition of the release of excitatory aminoacids;
- inhibition of GABA reuptake;
- stimulation of the proliferation and expression of GABA receptors;
- inhibition of the synthesis of folic acid;
- interference with metabolism of vitamin D;
- interference with activity of sexual hormones;
- interference with membrane lipids → produce membrane stabilization.

Pharmacodynamic effects:
- anticonvulsant effects (hydantoins control partial epilepsy and generalised tonic-clonic epilepsy; are used as part of the emergency treatment of status epilepticus);
- antiarrhythmic effects (Phenytoin is a class Ib antiarrhythmic drug);
- antifolate effects.

Pharmacokinetics:
- Phenytoin is 90% bound to plasma proteins. Hypoalbuminemia increases the concentration of unbound fractions. Plasma protein binding is reduced in renal disease.
- Hydantoins are metabolic enzyme inducers (stimulate hepatic metabolism of other drugs and even its metabolism).
- Phenytoin has saturable kinetics (saturable enzyme metabolism).

Indications:
- anticonvulsant for:
  - tonic-clonic seizures (grand mal epilepsy),
  - partial epilepsy,
  - status epilepticus (phenytoin iv and / or phenobarbital im are part of the status epilepticus treatment: they are administered after benzodiazepines);
- ventricular arrhythmias (it is used particularly for the treatment of acute intoxication with digitalis).
Adverse effects:
- nausea, diplopia, nystagmus, tremor, ataxia, headache, lethargy;
- hyperkinesia, choreoathetosis symptoms, paradoxical increase in seizure frequency;
- gingival hyperplasia;
- osteomalacia;
- megaloblastic anemia, agranulocytosis;
- immunological (allergic) reactions: fever, rash, exfoliative dermatitis;
- hirsutism (by modifying the metabolism of sex hormones);
- keloid formation;
- lymphadenopathy (a possible causal relationship to Hodgkin's disease);
- sedation at high doses;
- peripheral neuropathy, decreased deep tendon reflexes in the legs;
- coarsening of facial features;
- hepatotoxicity.

Drug interactions:
- Phenytoin has a high affinity for thyroid-binding globulin → false results in tests of thyroid function (evaluation of thyroid function in patients treated with Phenytoin is only by measurement of plasma concentrations of TSH).
- Hypoalbuminemia increases the concentration of free fractions of phenytoin, reduced total plasma concentrations of phenytoin → increasing the dose determines toxic concentrations of phenytoin.

Phosphenytoine is a prodrug, which is rapidly converted into Phenytoin in plasma; the administration is parenteral.

Ethotoin may be recommended for patients hypersensitive to Phenytoin, but the adverse effects are more severe than those of Phenytoin.

Mephenytoin is metabolized to nirvanol (an active metabolite); the adverse effects (dermatitis, agranulocytosis, hepatitis) are more severe than those of Phenytoin.

3. Tricyclic compounds: Carbamazepine, Oxcarbazepine

Carbamazepine was initially marketed for the treatment of trigeminal neuralgia but later proved efficacy for treating epilepsy. Carbamazepine is considered first generation antiseizure drugs.

Oxcarbazepine is considered second generation antiseizure drugs.

Mechanisms of action:
- block the voltage-gated sodium channels (selectively bind to the channel in the inactive state and reduce the ability of the channel to recover from inactivation);
- inhibit the release and reuptake of norepinephrine;
- interfere with adenosine receptors;
- possible potentiate the postsynaptic action of GABA.
Pharmacodynamic effects:
- anticonvulsant effects,
- antipsychotic effects,
- analgesic effects only for Carbamazepine.

Pharmacokinetics:
- Carbamazepine is metabolic enzyme inducer (stimulate hepatic metabolism of other drugs and even its metabolism).
- Oxcarbazepine is a prodrug; it has a longer duration of action through its active metabolite. Oxcarbazepine is less potent enzyme inducer than is Carbamazepine.

Indications:
- anticonvulsant for:
  - partial epilepsy simple and complex (Carbamazepine is first-choice drug);
  - tonic-clonic seizures (grand mal epilepsy),
- alternative treatment for bipolar psychoses (when lack of response to lithium salts);
- analgesic: trigeminal neuralgia (Carbamazepine is first-choice drug).

Adverse effects:
- the most common in initial therapy are:
  - ataxia\(^1\), diplopia,
  - gastro-intestinal symptoms: nausea, vomiting, anorexia, abdominal pain;
  - CNS effects: dizziness, drowsiness, headache;
- immunological reactions type I (rash, skin erythema, urticaria) or type II
- hyponatremia, sometimes edema;
  - Oxcarbazepine determines a more severe hyponatremia.
- very severe: idiosyncratic blood dyscrasias: agranulocytosis, aplastic anemia;
- rare: abnormalities of liver and kidney function, hepatitis, cholestatic jaundice.

Drug interactions
- Carbamazepine and Phenobarbital decreases steady-state concentration of Phenytoin by inducing CYP3A4.
- Phenytoin and Phenobarbital decrease steady-state concentrations of Carbamazepine by inducing CYP3A4.

4. Succinimides: Ethosuximide, Phensuximide, Methsuximide

Mechanisms of action:
- inhibit T-type calcium channels (in thalamic neurons);
- inhibit Na+/K+-ATPase;
- inhibit GABA – transaminase\(^2\) (GABA - T).

Pharmacodynamic effects: anticonvulsant effects.

Ethosuximide

Indications: absence seizures as first-choice drugs.

Adverse effects:
- gastro-intestinal symptoms: nausea, vomiting, anorexia, gastric upset, abdominal pain.

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\(^1\) Ataxia is the inability to coordinate muscle activity during voluntary movement.

\(^2\) GABA – transaminase is the short name of GABA aminotransferase, the enzyme involved in the degradation of GABA.
• CNS effects: drowsiness, dizziness, headache, transient lethargy, fatigue, mild euphoria, hiccups, behavioral changes,
• abnormalities of liver and kidney function,
• others: rash, thrombocytopenia (→ pancytopenia), eosinophilia; lupus erythematosus.

**Methsuximide**

*Indications:*
- absence seizures (treatment of choice),
- partial epilepsy (alternative treatment because of the high toxicity).

5. **Carboxylic acids:** Valproic acid, Sodium valproate, Divalproex (Divalproex is a combination of Sodium valproate and Valproic acid)

*Mechanisms of action:*
- block the voltage-gated sodium channels (selectively bind to the channel in the inactive state and reduce the ability of the channel to recover from inactivation);
- increase levels of GABA in brain:
  - inhibit GABA - transaminase;
  - inhibition of GABA transporter GAT-1, involved in the uptake of GABA;
  - increase the activity of glutamic acid decarboxylase (GAD), the enzyme responsible for GABA synthesis;
- block NMDA receptor-mediated excitation;
- decrease the concentration of aspartate in the brain;
- open and activate potassium channels in the neuronal membrane, which increase membrane potassium conductance determining membrane hyperpolarisation.

*Pharmacodynamic effects:* anticonvulsant effects.

*Indications:*
- as anticonvulsants:
  - absence seizures (drug of choice),
  - juvenile myoclonic epilepsy (as first-choice drug),
  - tonic-clonic seizures (grand mal epilepsy),
  - partial epilepsy, simple and complex;
- migraine prophylaxis;
- alternative treatment for bipolar psychoses.

*Adverse effects:*
- gastro-intestinal symptoms: nausea, vomiting, abdominal pain, "heartburn", increased appetite (has as consequence weight gain);
- transient alopecia (hair loss);
- tremors;
- sedation at high doses;
- hepatotoxicity: increase serum transaminases, hepatic necrosis, increase serum alkaline phosphatase; pancreatitis;
- thrombocytopenia may cause abnormal bleeding;
- teratogenic effects (administered during pregnancy increase the incidence of spina bifida, cardiovascular anomalies, orofacial and digital anomalies).
6. Oxazolidinediones: Trimethadione, Paramethadione, Dimethadione
Their use is limited today.
Mechanisms of action: inhibit T-type calcium channels (in thalamic neurons)
Pharmacokinetics: Trimethadione is metabolized to an active metabolite which exert major antiseizure activity and has long half-life.
Pharmacodynamic effects: anticonvulsant effects.
Indications: absence epilepsy.
Adverse effects:
- most common: sedation;
- metabolic acidosis;
- immunological effects type I (rash, exfoliative dermatitis) or type II (autoimmune nephrotic syndrome, myasthenia gravis);
- pancytopenia, night blindness, disorders of visual accommodation.

Indications:
- myoclonic epilepsy;
- infantile spasm;
- status epilepticus (benzodiazepines may be associated with ACTH or dexamethasone).
Mechanisms of action, pharmacodynamic effects, pharmacokinetics, indications, contraindications, side effects → see in Chapter "anxiolytic-sedative-hypnotics".

8. Bromides
Mechanisms of action, pharmacodynamic effects, pharmacokinetics, indications, contraindications, side effects → see in Chapter "anxiolytic-sedative-hypnotics".

9. Carbonic anhydrase inhibitors: Acetazolamide
Mechanisms of action:
- inhibition of carbonic anhydrase in the brain determine metabolic acidosis;
- inhibition of carbonic anhydrase in the eye;
- inhibition of carbonic anhydrase in the proximal convoluted tubule;
- inhibition of carbonic anhydrase in the gastric mucosa.
Pharmacodynamic effects:
- in the CNS → antiseizure and antiemetic effect;
- reduction of intraocular pressure;
- increased diuresis (alkaline diuresis);
- inhibiting the production of HCl.
Indications:
- anticonvulsant as alternative treatment for all types of epilepsy (tolerance to this effect appears after 4 weeks of treatment), it is the treatment of choice in women with seizure exacerbations at the time of menses;
- other indications: glaucoma; altitude sickness; metabolic alkalosis; as diuretic to alkalization of urine; ulcer disease.
Contraindications: renal failure and severe hepatic impairment, pregnancy.
Adverse effects:
- hyperchloremic metabolic acidosis;
- immunological reactions of type I and type III;
- hypokalemia;
- phosphaturia, hypercalciuria, hyperbicarbonaturia, formation of kidney stones;
- paresthesias in the limbs, disorders of the CNS in patients with renal insufficiency.

10. Other structures (second generation antiseizure drugs)
With the exception of felbamate and vigabatrin, second generation antiseizure drugs (eg, gabapentin, lamotrigine, topiramate, levetiracetam, pregabalin, lacosamide, zonisamide) have a number of potential advantages over older antiseizure drugs (eg, phenobarbital, phenytoin, carbamazepine, valproate):
- lower side-effect rates,
- little or no need for serum monitoring,
- once or twice daily dosing for some,
- fewer drug interactions.

Vigabatrin
The drug is a derivative of gamma-vinyl-GABA.
Mechanism of action: irreversible inhibition of GABA-T.
Pharmacodynamic effects: anticonvulsant effects.
Pharmacokinetics: saturable kinetics; bioavailability = 60%; the drug is not significantly related to plasma proteins; T1/2 = 6-8 hours; renal elimination.
Indications:
- partial epilepsy;
- West syndrome.
Adverse effects:
- weight gain;
- drowsiness, dizziness;
- rarely, psychomotor agitation, states of confusion, psychoses (the drug is contraindicated in patients with psychiatric disorders);
- visual field defects (1/3 of patients) – irreversible retinal toxicity;
- teratogenic.

Tiagabine
The drug is a derivative of nipecotic acid.
Mechanisms of action: inhibition of GABA transporter GAT-1, involved in the uptake of GABA in the neurons and glial cells → increased levels of GABA in the forebrain and the hypothalamus.
Pharmacokinetics: bioavailability = 100%; T1/2 = 5-8 hours (T1/2 is decreased in the presence of other antiepileptic drugs); foods decrease plasma concentrations; liver failure determines a decrease in clearance.
Indications:
- partial epilepsy;
- tonic-clonic seizures (grand mal epilepsy).
Adverse effects: dizziness; drowsiness; asthenia; ataxia; confusional state; nervousness; tremors; difficulties in concentrating; depressive states; emotional lability; psychoses; rash.
Gabapentin
The drug is an analogue of GABA.
**Mechanism of action:** modulation of synaptic release and metabolism of GABA or GABA reuptake by GABA transporters.
**Pharmacokinetics:** the drug is not metabolized; linear elimination kinetics; renal elimination; T1/2 = 5 to 8 hours.
**Indications:**
- partial epilepsy;
- epilepsy grand mal;
- as an analgesic in neuropathic pain (including postherpetic neuralgia).
**Adverse effects:** somnolence, drowsiness, dizziness, headache, fatigue, tremor, ataxia. The adverse effects usually are mild and disappear within 2 weeks after start of treatment.

Lamotrigine
The drug is a derivative of phenyltriazine.
**Mechanism of action:** block the voltage-gated sodium channels (selectively bind to the channel in the inactive state and reduce the ability of the channel to recover from inactivation).
**Pharmacokinetics:** the plasma protein binding = 55% (approximately); metabolism in the liver by glucuronidation; renal elimination; saturable kinetics; T1/2 = 24 hours (it is 13 to 15 hours in the presence of metabolic enzyme inducers).
**Indications:**
- partial epilepsy;
- juvenile myoclonic epilepsy;
- absence seizures (probably, the drug also acts on calcium channels).
**Adverse effects:** nausea; headache; drowsiness, dizziness; diplopia; rash; dermatitis (1-2%).

Topiramate
The drug is a substituted monosaccharide.
**Mechanisms of action:**
- block the voltage-gated sodium channels (selectively bind to the channel in the inactive state and reduce the ability of the channel to recover from inactivation);
- potentiation of the inhibitory effect of GABA at other sites than the barbiturate or benzodiazepine site;
- inhibit the action of kainate on AMPA receptors.
**Pharmacokinetics:** saturable kinetics; bioavailability = 80%; the drug is bound to plasma proteins → 15%; T1/2 = 20 to 30 hours; metabolism = 20 - 50%; the drug decreased plasma concentrations of estrogens.
**Indications (monotherapy):**
- partial epilepsy;
- tonic-clonic seizures (grand mal epilepsy).
**Adverse effects:** drowsiness; dizziness; fatigue; decreased cognitive function; paresthesia; nervousness; confusional state; urolithiasis (15%); teratogenicity.

Zonisamide
The drug is a sulfonamide derivative.
**Mechanisms of action:**
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- block the voltage-gated sodium channels (selectively bind to the channel in the inactive state and reduce the ability of the channel to recover from inactivation);
- block voltage-dependent calcium channels.

**Pharmacokinetics:** the kinetics is linear. Good bioavailability. T1/2 = 1-3 days.

**Indications:**
- partial epilepsy;
- tonic-clonic seizures (grand mal epilepsy);
- infantile spasm;
- myoclonus.

**Adverse effects:** drowsiness; damage cognitive function; kidney stones; rash.

**Pregabalin**

**Mechanisms of action:** block the voltage-gated sodium channels.

**Indications:**
- partial epilepsy;
- neuropathic pain (associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia);
- generalised anxiety disorder.

**Adverse effects:** drowsiness; blurred vision, weight gain, peripheral edema.

**Felbamate**

**Mechanism of action:**
- block NMDA receptors;
- block voltage-dependent sodium channels;
- block calcium channels;
- potentiate GABA actions.

**Pharmacokinetics:** metabolism in the liver by hydroxylation and glucuronidation.

**Indications:**
- Lennox-Gastaut syndrome;
- partial epilepsy (the third line of treatment due to toxicity).

**Adverse effects:** severe hepatitis; aplastic anemia.

**Drug interactions:**
- Felbamate determines the increase in plasma levels of Phenytoin and Valproic acid,
- Felbamate determines the decrease in plasma levels of carbamazepine.

**Levetiracetam**

The drug is an analogue of Piracetam.

**Mechanisms of action:**
- allosteric modulation of GABA receptor,
- modulation of high-voltage activated Ca2+ channels and some K+ channels.

**Pharmacokinetics:** the kinetics is linear. T1/2 = 6-8 hours, approximately. It is prolonged in the elderly.

**Indications:** adjunct therapy of partial seizures, myoclonic seizures, and generalized tonic-clonic seizures.

**Adverse effects:** drowsiness, fatigue, dizziness.