Antiepileptic drugs
**Epilepsy**

**Definition:**
- **Epilepsy** is a common chronic neurological disorder characterized with occurrence of recurrent **seizures**
- **Seizures** are transient brain dysfunctions induced by episodic high-frequency discharge of impulses by a group of neurons in the brain.
- Rather than single disease, epilepsy might viewed as a family of brain disorders sharing the common manifestation by seizures.

**Compare relationship**
- Epilepsy vs. seizures
- Epileptic seizure vs. convulsions
- Convulsions vs. epileptic seizures

**Epidemiology:** it affects 0.5-1% of the population.

**Etiology:** very heterogeneous.
- Often idiopathic
- **Brain damage** (trauma, infection, stroke, intoxication or tumor growth)
- Inherited neurological syndromes or other kinds of neurological disease

**Provocation of seizures:** flashing light, hypoglycemia, fever, drugs and sudden withdrawal of antiepileptics

**Diagnosis** – EEG, Diff. Diagnosis – drug intoxications (e.g., isoniazid), withdrawal syndrome (benzodiazepines, barbiturates, alcohol).
Classification of epileptic seizures

• The clinical manifestation of epileptic seizures principally depends on the brain area affected.

• According to the pathological discharge localization we distinguish:
  • partial seizures
  • generalized seizures

- According to the level of consciousness being present we distinguish:
  • simple seizures (consciousness is NOT lost)
  • complex seizures (consciousness IS lost).
Partial seizures

- The discharge begins locally, and often remains localised.
- The symptoms strictly depend on the brain region(s) involved.
- It is typically confined to single brain hemisphere.

**Simple partial:**
- The consciousness is preserved.
- Duration: 0,5-3 min.
- Clinical manifestations at level of:
  - **Motor functions:** jerking, spasms or rigidity of the particular muscle groups.
  - **Perception:** bizarre or strange sensory experience (visual, taste or olfactory).
  - **Mood and behavioral:** fear, „deja-vu“, flare of anger, emotional outbursts.
- **Jacksonian epilepsy:** repetitive jerking of a particular muscle group, which spreads and may involve much of the body within 2 minutes before dying out.

**Complex partial** *(psychomotor epilepsy, temporal lobe epilepsy)*
- Lost of consciousness.
- Often preceded with „aura“.
- Stereotype behavior (often bizarre) - dressing, walking, crumpling, smacking, hair combing. After few minutes the patients recovers, however, without recollection of the event.

**Secondarily generalised**
- Starting as partial and degenerate to the generalised forms.
Generalised seizures

- Involve the whole brain
- Immediate loss of consciousness is a characteristic feature

**Tonic-clonic seizures** (*grand mal*)
- Duration 1-3 min
  - **Tonic Phase** (up to 1 min): an initial strong contraction of the whole musculature, causing a rigid extensor spasm and fall. Respiration stops and defecation, micturation and salivation often occur.
  - **Clonic Phase** (2-4 min): a series of violent, synchronous jerks.
  - The patient gradually recovers, feeling tired and confused. Total amnesia is present. Injury may occur during the convulsive episode.

**Absence seizures** (*petit mal*)
- are much less dramatic
- may occur with high frequency
- The patient
  - abruptly ceases whatever he or she was doing, sometimes stopping speaking in mid-sentence
  - and stares vacantly for a few sec (blinking), with little or no motor disturbance.
  - The patient is unaware of his or her surroundings and recovers abruptly with no after-effects
- Typically in children – impaired learning capabilities

Other types: Myoclonic s. (isolated- shock-like jerks), Tonic s. (muscle rigidity) Atonic s.
**Status epilepticus**

- Most of epileptic seizures are terminated spontaneously
- Status epilepticus is, however, the exception and therefore, it presents an **emergency situation**

**Definition SE:**
- A clinical status where the seizure is abnormally prolonged
- or when one seizure skips to another one (repeatedly) without patient becoming conscious

- The most dangerous form is its **generalised convulsive form** (GCSE)
  - It is accompanied with significant morbidity and mortality (5-15%)
    - There is a negative energy balance in the brain
    - In addition to: respiratory insufficiency and hypoxia
    - Hyperthermia and rhabdomyolysis
    - High secretion of catecholamines induce hypertension, tachycardia, cardiac arrhythmias, and hyperglycemia

- Diff. Diagnostics: intoxications, withdrawal syndrome (e.g., BZD).
Therapy of epilepsy

- **Pharmacotherapy is a basic therapeutic approach**
- **AIM**: to prevent or at least significantly reduce the frequency and severity of seizures
- Treatment is typically *long-lasting* (even life-long)
  - Consider demands on safety and tolerability, inc. teratogenicity
- We do NOT treat *acute seizure* (except for status epilepticus)
- Unfortunately, pharmacotherapy is **NOT a causal** approach
- However, significantly **improve the quality of life** (destigmatization, ability to work etc) and prevent development of further CNS deteriorations
- **Monotherapy** is the preferable approach
  - The combination treatments can be complicated by PK and PD interactions
  - Before the combination of antiepileptics drug is responsibly started, monotherapy with several (2-3) drugs should be tested
  - When combination treatment is needed:
    - limit the number of drugs on 2 whenever it is possible
    - prefer to add drugs free of significant PK or PD interactions (to keep the treatment manageable)
Therapy of epilepsy

• Current antiepileptic drugs are effective in controlling seizures in about 75% of patients
  – In 50% of patients we obtain nearly complete eliminations of seizure occurrence
  – In additional 25% of patients we can significantly reduce the frequency and severity of seizures

• The choice of drugs is based on type of seizures, tolerability of a drug and response to therapy (empiric part)

• The therapy is often started with the lower dose and the dose is „titrated“ gradually thereafter

• The use of antiepileptics is often limited by their adverse effects
Antiepileptic drugs
Mechanisms of actions

• **Enhancement of GABA-ergic action**
  phenobarbital, benzodiazepines, vigabatrin, gabapentin

• **Inhibition of sodium channel function**
  (reduction of electrical excitability of cell membranes)
  phenytoin, carbamazepine, valproate, lamotrigine

• **Inhibition of calcium channel function** *(T-type calcium channels)*
  ethosuximide, gabapentin
Enhancement of GABA-ergic inhibition

Results into membrane hyperpolarisation and increase of AP threshold

• Benzodiazepines, barbiturates

• Vigabatrin – irreversible inhibition of transaminases (GABA inactivating enzymes)

• Tiagabine – GABA re-uptake inhibition

• Valproate – inhibits among other GABA-transaminase and succinic-semialdehyde-dehydrogenase

• This mechanism is **NOT** valid for Gabapentin! Although originally designed as GABA-derivative

*Goodman and Gillman’s The Pharmacological Basis of Therapeutics, 2006.*
Voltage gated Na+ channel Inhibition

- Phenytoin
- Carbamazepine
- Lamotrigine
- Valproate
- Topiramate?
- Zonisamide?

USE DEPENDENCE:
3 conformation forms
Of Na channels:

"resting"
inactive → active

Goodman and Gillman’s The Pharmacological Basis of Therapeutics, 2006.
Ca$^{2+}$ Channel inhibition

- T-type Ca$^{2+}$ channel inhibition
  - Ethosuximide
  - Valproate (?)
  - Pacemaker current reduction (participating on absence development)
  - Gabapentin

- Combination of different mechanisms
  - E.g., topiramate
  - Incl. also Glutamate transmission inhibition

Goodman and Gillman’s The Pharmacological Basis of Therapeutics, 2006.
Pharmacokinetics of antiepileptic drugs

Is often unusually **complicated** → importance of TDM

- Nonlinear pharmacokinetics (0. order) – phenytoin
- Impact on activity of biotransformation enzymes
  - CYP Inducers: phenobarbital, phenytoin, primidone, carbamazepine
  - CYP Inhibitors: valproate, topiramate
  - Impact on **UDP-glucuronide transferase (UGT)**
    - inhibitors – valproate
    - inducers - lamotrigine, phenobarbital, phenytoin, carbamazepine
- Strong plasma protein binding – interactions!
  - determination of (free) unbound fraction, which determines the therapeutic and toxic effects, might be of value
  - Combinations like valproate + phenytoin might be troublesome
Antiepileptics - indications

• Often used antiepileptics with broad indication spectrum (with exception of absences):
  – Carbamazepine, valproate, lamotrigine, phenytoin

• Partial seizures
  – Carbamazepine, phenytoin, valproate, lamotrigine
  – Alternatives: gabapentin, topiramate, tiagabine

• Tonic-clonic (grand mal)
  – phenytoin, carbamazepine, valproate
  – Alternatives: lamotrigine, topiramate, phenobarbital (primidone)

• Absence (petit mal)
  – Ethosuximide
  – Valproate – especially in the case that tonic-clonic seizures are also present
  – Alternatives: lamotrigine

• Myoclonic
  – clonazepam, valproate
  – Alternatives: lamotrigine
Antiepiletics - indications

Modified according to: E. Nešpor. Remedia 2003,6:409-415
Barbiturates

- Mech. of action, PK, IND, CI, Adv. eff., intoxication.... You should already know this!
- **Phenobarbital**
  - 1st antiepileptic drug ever developed
  - Antiepileptic actions is seen in most of barbiturates, however, phenobarbital shows antiepileptic action in lower concentrations with acceptable degree of sedation
  - **Adverse reactions** (dose dependent):
    - sedation (although a degree of tolerance develops), decreased cognitive and motoric functions.
  - Barbiturates were largely displaced from every day clinical practice with phenytoin and with recent antiepileptics (which are better tolerable esp. with regard on sedative effects)
  - **Induction of CYP 450 is present**

- **Primidone**
  - Is mainly bioactovated into phenobarbital
  - Induction of CYP 450 is present
Benzodiazepines

- Mech. of action, PK, Ind, Clnd, Adv. eff., intoxication.... You should already know all of this!

- **Clonazepam**
  - Is among drugs of choice in **myoclonic seizures**
  - May be an alternative in some other seizures
  - Is an alternative to diazepam (i.v.) in status epilepticus treatment
  - **Disadvantage** – the **tolerance develops on the effects**
  - Adverse effects: sedation (dose dependent), paradox excitation might sometimes occur

- **Diazepam**
  - i.v. in **status epilepticus treatment** (rapid onset of action, redistribution may cause quite rapid decrease of effectiveness)
  - **Lorazepam** (i.v., an alternative to diazepam in SE treatment, slower onset but longer duration of action)

- **Clobazam**
Phenytoin

- A derivative of hydantoin
  - originally derived from barbiturates
  - but there is a different mech. of action to barbiturates and there is also no sedative/hypnotic action

- Mech. of action: Na\(^+\) channels inhibitions (use dependence)

- PK: 0. order with high inter- and intraindividual variability → often problems with predictability of the response
  - Good absorption from GIT (almost complete)
  - More than 90% is plasma protein bound – interaction e.g., with valproate
  - Biotransformation – CYP 2C (saturable) → inactive metabolites
  - Pharmacokinetics 0. order – small change in dose → unpredictably high change in plasma concentrations (toxicity)!
  - Induction of CYP a UGT– decreased plasma concentrations and clinical effects of drugs administered concomitantly
  - Attention should be paid e.g., in hormonal contraception or warfarin

- Be careful about generic prescription !
- Rather avoid in combination regimens !
Antiepileptic drugs
Phenytoin

**Adverse effects Type A** (*dose-related*)
- vertigo, ataxia (lower Cpl),
- confusion with intellectual deterioration (higher Cpl)
- gums hyperplasia (gradual development, disfiguring)
- hirsutism (gradual development, androgen secretion)
- megaloblastic anemia (in deficiency of folic acid)

Minor effect on cognition and vigility (**virtually no sedation**!)

**Adverse effects Type B** (*not dose-related*) quite common
- **allergy:** rashes (quite common)
- idiosyncrasy: hepatitis (rather rare)

**Adverse effects Type D - TERATOGENICITY**
the increased incidence of fetal malformations in children born to epileptic mothers
"fetal hydantoin syndrom", particularly the occurrence of cleft palate (epoxide metabolite?)
Carbamazepine

- Derived from TCA (imunostilben structure)
- Widely used in clinical practice (also in neuropathic pain and bi-polar disorder!)
- PK
  - well absorbed
  - a powerful inducer of hepatic CYP450
  - Autoinduction → plasma half-life is becoming shorter
  - Heteroinduction → accelerates biotransformation of many other drugs (phenytoin, warfarin) → DRUG INTERACTIONS!
  → the combination with other antiepileptic drugs should be rather avoided

ADVERSE EFFECTS:
Relatively well tolerable drug, although different adverse reaction may occur

- **Adverse effects Type A** (*dose-related*)
  - low incidence
  - drowsiness, dizziness, ataxia
  - more severe mental and motor disturbances, water retention
  - to avoid it: treatment is usually started with a low dose

- **Adverse effects Type B** (*not dose-related*)
  severe bone-marrow depression (very rare)

- **Risk of teretogenicity** is significant
Valproate

- Is not related to any known antiepileptic drug (discovered by chance)
- VERY broad spectrum drug (esp. in children)
  - The only drug effective in both grand and petit mal!
  - Besides antiepileptic effects, it might be also used in psychiatry as a „mood stabilizer“ (with advantage where epilepsy is present as comorbidity)
- Of relatively low toxicity (low frequency of adverse reactions)
- **Mechanism of action:** complex and not entirely clear (Na⁺ channel inhibition, GABA degradation inhibition....)
- **PK:** high degree of plasma protein binding, CYP450 inhibition, it is excreted in urine as a metabolite
- **Adverse reactions:** only minimal sedative action, reversible alopecia, weight gain, increased probability of bleeding, severe hepatotoxicity is very rare.
- **Teratogenicity**!!!! Defect of neural tube (spina bifida). Might be better to consider an alternative in females in reproductive age.
- Might be combined with ethosuximide in absences
Ethosuximide

• Drug of choice in absences (inactive in other seizures)
• **Mechanism of action:** T-type Ca\(^{2+}\) channel inhibition
• **PK:** good oral absorption, biotransformation in the liver to inactive metabolites
• **Adverse reactions:** (well tolerable in optimal dosage)
  – Dose dependent: CNS - drowsiness, headache, fatigue, GIT – nausea, vomiting (in up to 40% of patients)
  – Dose independent: idiosyncratic reactions – „lupus like“, hematopoietic disturbances
Newer antiepileptics
(3rd Generation)

- **Lamotrigin** – Na+ channel inhibition
  - Broad spectrum in epilepsy treatment
  - Good response in monotherapy (may be drug of choice or often an „alternative of choice“)
  - **Might be good for combinations** (dose adaptation in drugs affecting biotransformation may be necessary – phenytoin x valproate)
  - Well tolerable
  - Without PK abnormalities = relatively **well predictable effect**.
  - **Adverse reactions**: Dose dependent: CNS – ataxia, headache, diplopia; idiosyncratic skin reaction; aggressivity provocation

- **Vigabatrin** – irreversible GABA-transaminase inhibition
  - Irreversibility of inhibition is given by transfer of vinyl-group on enzyme
  - Response might be obtained even in some types of **epilepsy refractory** to other treatment
  - **WITHOUT PK interactions**
  - Relatively well tolerable, Rare induction of **acute psychotic reactions** was observed (reversible)
  - **Visual disturbances** (esp. disturbances of the perimeter – visual field), monitoring by ophthalmologist is recommended
Newer antiepileptics (3rd Generation)

• **Tiagabine** – GABA re-uptake inhibitor
  – Free of PK abnormalities
  – Adverse reaction: usually only common CNS related ones (depend on the drug dose)

• **Gabapentin**
  – Designed as a GABA analogue which would have a good distribution into the CNS
  – But surprisingly it is **NOT an agonist on GABA receptors** and it does not affect GABA-ergic transmission at all
  – → **what is the mechanisms of action?**
    • T-type Ca\(^{2+}\) channel inhibition?
  – Adverse reaction: CNS – expectable (but not serious) + **aggressivity in children**
  – Relatively low response in monotherapy
  – Relatively **low risk of PK interactions** and good safety profile enables its employment in **combination treatments**
Newer antiepileptics
(3rd Generation)

• **Topiramate**
  - Mechanism of action: likely complex (combination of number previously mentioned effects)
  - Broad indication spectrum
  - Relatively well tolerable drug
  - Adverse reactions: anorexia, cognitive function impairment
  - Contraindication: gravidity

• **Levetiracetam**
  - An analogue to nootropic drug piracetam
  - Antiepileptic mechanism of action is unknown (it is not the common one)
  - Free of serious PK interactions
  - Relatively well tolerable

• **Zonisamide**
  - Antiepileptic mechanism of action in not sure
    - Blocks Na+ channels to some extent
Antiepileptic drugs withdrawal

• Can cause increased seizure frequency and severity.
• In general, barbiturates and benzodiazepines are the most difficult to discontinue. Weeks or months may be required, with very gradual dosage decrements, to accomplish their complete removal.

• Complete discontinuance is an especially difficult problem. If a patient is seizure-free for 3-4 years, gradual discontinuance might be considered.
Antiepileptic drugs and teratogenicity

- The potential teratogenicity of antiepileptic drugs is controversial and important topic.
  - long-term drug treatment of million of people is a reality
  - Children born to mothers taking antiepileptic drugs have an increased risk, perhaps twofold, of congenital malformation.

- Phenytoin has been implicated in a specific syndrome called “fetal hydantoin syndrom“.

- A similar syndrome has been attributed both to phenobarbital and to carbamazepine.

- Valproate has also been implicated in a specific malformation - spina bifida.