Epilepsy – Part I.

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Scheme of the lecture

Epilepsy - Part I.
• Epidemiology
• Definition
• Pathomechanism
• Classification
• Diagnostics
• Differential diagnostics

Epilepsy - Part II.
• Therapy
• Status epilepticus
EPILEPSY: EPIDEMIOLOGY
Epidemiology: Epilepsy

Epilepsy affects **50 million people** worldwide.

The **prevalence** of epilepsy is: cca. 1%

The **incidence** of epilepsy is: 44 cases per 100,000 person years

(in both sexes)

Genders:
- in females: at 41 cases per 100,000 person years
- for males: at 49 cases per 100,000 person years

**The Rochester Epilepsy Study/Epidemiology Project (1996):**
- prevalence of epilepsy: male 6.5 vs. female 6.0 per 1000 persons

The **risk for recurrent seizure** is similar between males and females, as is the likelihood of ultimate **remission of epilepsy**.

http://emedicine.medscape.com/
Famous People with Epilepsy

- Vladimir Lenin - Politician
- Florence Griffith Joyner - Athlete
- Fyodor Dostoyevsky - Author
- Prince - Musician
- Neil Young - Musician
- Bud Abbot (Actor - Abbott and Costello)
- Danny Glover - Actor
- Retrospective Diagnosis:
  - Napoleon I
  - Socrates
  - Julius Caesar
  - Joan of Arc

Also: Susan Boyle and Prince
EPILEPSY: DEFINITION
Definition: Epilepsy

Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition.
Epilepsy // Seizures

Nota bene!

SEIZURE ≠ EPILEPSY

but:

EPILEPSY IS A SEIZURE DISORDER
Definition: What is epilepsy?

**Epilepsy** is a neurological (brain) disorder in which nerve cell activity in the brain becomes disrupted, causing **seizures** or periods of unusual behavior, sensations and loss of consciousness.

**Cortical neuronal hyperexcitability** - (firing/spiking on EEG) during a seizure

**Seizure symptoms** can vary widely:
- simply stare blankly - i.e. *absence* (for a few seconds)
- repeatedly twitch arms and/or legs - i.e. *convulsions* (for minutes)

*At least** two unprovoked seizures** are required for an epilepsy diagnosis.*
Definition of epilepsy
(ILAE: International League Against Epilepsy, 2014)

Operational (Practical) Clinical Definition of Epilepsy

1. **At least two unprovoked (or reflex) seizures** occurring more than 24 hours 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, occurring over the next 10 years;**

3. Diagnosis of an **epilepsy syndrome**

Epilepsy is considered to be resolved for individuals who had age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

http://www.ilae.org/
EPILEPSY: PATHOMECHANISM
Epilepsy: Pathomechanism

is not clear

Theories are:

• cellular and network mechanisms
• ionchannels / channelopathies
• neurotransmitters (Glutamate, GABA)
• receptors
• gene expressions
Epilepsy: Genetics
# Epilepsy: Genetics

## TABLE 1. MONOGENIC FORMS OF EPILEPSY SYNDROMES AND ASSOCIATED GENES

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Associated Genes</th>
<th>Function/gene product</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEFS+</td>
<td>SCN1A, SCN2A, SCN1B, GABRD, GABRG2</td>
<td>Subunits of voltage gated sodium channel, GABA receptor subunits</td>
</tr>
<tr>
<td>ADNFLE</td>
<td>CHRNA4, CHRNA2, CHRNB2</td>
<td>Subunits of nicotinic acetyl choline receptor</td>
</tr>
<tr>
<td>JME</td>
<td>EFHC1</td>
<td>Cortical development, neurotransmitter release</td>
</tr>
<tr>
<td></td>
<td>GABRA1</td>
<td>GABA receptor subunits</td>
</tr>
<tr>
<td></td>
<td>CACNB4</td>
<td>Subunit of calcium channel</td>
</tr>
<tr>
<td></td>
<td>CLCN2</td>
<td>Subunit of chloride channel</td>
</tr>
<tr>
<td>FLTLE</td>
<td>LGI1, SCN1A, SCN1B</td>
<td>Regulation of K channel and AMPA receptors, Subunits of voltage gated sodium channel</td>
</tr>
<tr>
<td>FMTLE</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

EPILEPSY: CLASSIFICATION
## Epilepsy: Classification

<table>
<thead>
<tr>
<th>Main category</th>
<th>Subcategory</th>
<th>Examples*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic epilepsy</td>
<td>Pure epilepsies due to single gene disorders</td>
<td>Benign familial neonatal convulsions; autosomal dominant nocturnal frontal lobe epilepsy; generalized epilepsy with labile seizures; severe myoclonic epilepsy of childhood; benign adult familial myoclonic epilepsy</td>
</tr>
<tr>
<td>Idiopathic epilepsy</td>
<td>Pure epilepsies with complex inheritance</td>
<td>Idiopathic generalized epilepsy (and its subtypes); benign partial epilepsies of childhood</td>
</tr>
<tr>
<td>Symptomatic epilepsy</td>
<td>Predominantly genetic or developmental causation</td>
<td>West syndrome; Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>Symptomatic epilepsy</td>
<td>Predominantly genetic or developmental causation</td>
<td>Unverricht-Lundborg disease; Dandy-Walker syndrome</td>
</tr>
<tr>
<td>Neurocutaneous syndromes</td>
<td>Other neurologic single gene disorders</td>
<td>Aicardi syndrome; tuberous sclerosis; Epilepsy; Sturge-Weber syndrome</td>
</tr>
<tr>
<td>Other neurologic single gene disorders</td>
<td>Tuberous sclerosis; neurocutaneous syndrome</td>
<td>Aicardi syndrome; tuberous sclerosis; Epilepsy; Sturge-Weber syndrome</td>
</tr>
<tr>
<td>Disorders of chromosome function</td>
<td>Developmental anomalies of cerebral structure</td>
<td>Down syndrome; Fragile X syndrome; NF-1 syndrome; leukaemic chromosome 15; ring chromosome 20</td>
</tr>
<tr>
<td>Predominantly acquired causation</td>
<td>Hippocampal sclerosis</td>
<td>Hippocampal sclerosis</td>
</tr>
<tr>
<td>Perinatal and infantile causes</td>
<td>Neocortical seizures; postneonatal seizures; cerebral palsy; vaccination and immunisation</td>
<td></td>
</tr>
<tr>
<td>Cerebral trauma</td>
<td>Open head injury; closed head injury; neurosurgery; epilepsy after epilepsy surgery; nonaccidental head injury in infants</td>
<td></td>
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<tr>
<td>Cerebral tumor</td>
<td>Gliomas; ganglioglioma; hamartomas; DNET; hypoplastic hamartoma; meningeal; secondary tumors</td>
<td></td>
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<tr>
<td>Cerebral infection</td>
<td>Viral meningitis and encephalitis; bacterial meningitis; abscess; malaria; necrocytosis, subcortical; HIV</td>
<td></td>
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<tr>
<td>Cerebrovascular disorders</td>
<td>Cerebral haemorrhage; cerebral infarction; degenerative vascular disease; arteriovenous malformations; cavernous hemangioma</td>
<td></td>
</tr>
<tr>
<td>Cerebral immunologic disorders</td>
<td>Rasmussen encephalitis; SLE and collagen vascular disorders; inflammatory and immunologic disorders</td>
<td></td>
</tr>
<tr>
<td>Degenerative and other neurologic conditions</td>
<td>Alzheimer’s disease and other demyelinating disorders; multiple sclerosis and demyelinating disorders; hydrocephalus and porencephaly</td>
<td></td>
</tr>
<tr>
<td>Provoked epilepsy</td>
<td>Provoking factors</td>
<td>Fever; menstrual cycle and carotid epilepsy; sleep–wake cycle; metabolic and endocrine-induced seizures; drug-induced seizures; alcohol and toxin-induced seizures</td>
</tr>
<tr>
<td>Reflex epilepsies</td>
<td>Photostimulational epilepsy; startle-induced epilepsies; reading epilepsy; auditory-induced epilepsy; eating epilepsy; hot-water epilepsy</td>
<td></td>
</tr>
</tbody>
</table>

**Table notes:**
- DNET, dysembryoplastic neuroovaltic tumor.
- These examples are not comprehensive, and in every category there are other causes.
- By definition, the causes of the cryptogenic epilepsies are \"unknown.\" However, there are important causes, accounting for at least 40% of epilepsies encountered in adult practice and a lesser proportion in pediatric practice.

*This list is derived from the book *Causes of Epilepsy* (Shorvon et al., 2011).*
<table>
<thead>
<tr>
<th>Main category</th>
<th>Subcategory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic epilepsies (15-20%)</strong></td>
<td>Pure epilepsies</td>
</tr>
<tr>
<td></td>
<td>due to single gene disorders</td>
</tr>
<tr>
<td></td>
<td>Pure epilepsies</td>
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<tr>
<td></td>
<td>with complex inheritance</td>
</tr>
<tr>
<td><strong>Symptomatic epilepsies (80-85%)</strong></td>
<td></td>
</tr>
<tr>
<td>Predominantly genetic or development</td>
<td>• Childhood epilepsy syndromes</td>
</tr>
<tr>
<td></td>
<td>• Neurocutaneous syndromes</td>
</tr>
<tr>
<td></td>
<td>• Disorders of chromosome function</td>
</tr>
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<td></td>
<td>• Developmental anomalies of cerebral structure</td>
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<tr>
<td>Predominantly acquired causation</td>
<td>• Hippocampal sclerosis</td>
</tr>
<tr>
<td></td>
<td>• Cerebral trauma</td>
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<td></td>
<td>• Cerebral tumor</td>
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<td></td>
<td>• Cerebral infection</td>
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<tr>
<td></td>
<td>• Cerebral vascular disorders</td>
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<tr>
<td></td>
<td>• Cerebral immunologic disorders</td>
</tr>
<tr>
<td></td>
<td>• Neurodegenerative disorders</td>
</tr>
<tr>
<td></td>
<td>• Others</td>
</tr>
<tr>
<td><strong>Provoked epilepsies</strong></td>
<td>Provoking factors</td>
</tr>
<tr>
<td></td>
<td>Reflex epilepsies</td>
</tr>
<tr>
<td><strong>Cryptogenic epilepsies (40%)</strong></td>
<td>by definition: the causes of the cryptogenic epilepsies are “unknown”</td>
</tr>
<tr>
<td></td>
<td>However, these are an important category, accounting for at least 40% of epilepsies encountered in adult practice (and a lesser proportion in pediatric practice).</td>
</tr>
</tbody>
</table>
### Provoked seizures/epilepsy

<table>
<thead>
<tr>
<th>Provoked epilepsy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoking factors</td>
<td></td>
</tr>
<tr>
<td>• Fever</td>
<td></td>
</tr>
<tr>
<td>• Menstrual cycle and catamenial epilepsy</td>
<td></td>
</tr>
<tr>
<td>• Sleep-wake cycle</td>
<td></td>
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<tr>
<td>• Metabolic and endocrine-induced seizures</td>
<td></td>
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<tr>
<td>• Drug-induced seizures</td>
<td></td>
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<tr>
<td>• Alcohol and toxin-induced seizures</td>
<td></td>
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<tr>
<td>• AED withdrawal</td>
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<tr>
<td>Reflex epilepsies</td>
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<tr>
<td>• Photosensitive epilepsies</td>
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<tr>
<td>• Startle-induced epilepsies</td>
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<tr>
<td>• Reading epilepsy</td>
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<tr>
<td>• Auditory-induced epilepsy</td>
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<td>• Eating epilepsy</td>
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<td>• Eating epilepsy</td>
<td></td>
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<tr>
<td>• Hot-water epilepsy</td>
<td></td>
</tr>
</tbody>
</table>
Drugs which can cause seizures

**Antibiotics**
- Penicillin's
- Isoniazid
- Metronidazole

**Anesthetics, narcotics**
- Halothane, enflurane
- Cocaine, fentanyl
- Ketamine

**Psychopharmaceuticals**
- Antihistamines
- Antidepressants
- Antipsychotics
- Tricyclic antidepressants

*Status epilepticus*
Epilepsy: Classification (etiology)

<table>
<thead>
<tr>
<th>Previous terms</th>
<th>Revised terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic / Primary</td>
<td>Genetic</td>
</tr>
<tr>
<td>Symptomatic / Secondary</td>
<td>“Structural/Metabolic”</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>Unknown cause</td>
</tr>
</tbody>
</table>
Epilepsy: Classification

FOCAL

GENERALIZED

CRYPTOGENIC

localisation axis

etiology axis

PRIMARY  SECONDARY
Seizures: Classification

• Generalized seizures
  • Tonic–clonic (in any combination)
  • Absence
    • Typical
    • Atypical
    • Absence with special features
      • Myoclonic absence
      • Eyelid myoclonia
  • Myoclonic
    • Myoclonic
    • Myoclonic-atonic
    • Myoclonic-tonic
  • Clonic
  • Tonic
  • Atonic

• Focal seizures
  Frontal/Temporal/Parietal/Occipital lobe symptoms
  • Without impairment of consciousness or awareness („Simplex partial seizures“)
  • With impairment of consciousness or awareness („Complex partial seizures“)

• Unknown (Unclassified) seizures
  e.g., Epileptic spasms

Berg AT et al Epilepsia 2010
# Electro-clinical epilepsy syndromes

## Age-dependent

<table>
<thead>
<tr>
<th>Period</th>
<th>Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td></td>
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<tr>
<td>Infancy</td>
<td></td>
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<tr>
<td>Childhood</td>
<td></td>
</tr>
<tr>
<td>Adolescence</td>
<td>Juvenile absence epilepsy,</td>
</tr>
<tr>
<td>Adult</td>
<td>Juvenile myoclonic epilepsy,</td>
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<tr>
<td></td>
<td>Progressive myoclonic epilepsy, etc.</td>
</tr>
</tbody>
</table>

## Not age-dependent

<table>
<thead>
<tr>
<th>Distinctive constellations</th>
<th>Mesial TLE with hippocampal sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rasmussen syndrome</td>
</tr>
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<td></td>
<td>Gelastic seizures with hypothalamic hamartoma</td>
</tr>
<tr>
<td></td>
<td>etc.</td>
</tr>
</tbody>
</table>

| Epilepsies with structural-metabolic causation | Malformations of cortical development (hemimegalencephaly, heterotopias, focal cortical dysplasia, etc.) |
|                                                | Neurocutaneous syndromes/Phacomatoses (sclerosis tuberosa, Sturge-Weber syndrome, etc.) |
|                                                | Tumor / Infection / Trauma / Stroke |
|                                                | Perinatal cerebral insults          |

| Epilepsies of unknown cause („cryptogenic”) | Benign neonatal seizures |
|                                            | Febrile seizures            |

<table>
<thead>
<tr>
<th>Others</th>
<th></th>
</tr>
</thead>
</table>

Berg AT et al *Epilepsia* 2010
St Valentines
is the Patron Saint of Epilepsy
Happy
(Seizure Free)
Valentines
Day

©EpilepsyHackney #HelpMakeEpilepsyStandOut Sept 2013
EPILEPSY: DIAGNOSTICS
Epilepsy (Seizure): Diagnostics

• **Medical history**
  • Auto / **Heteroanamnensis** (eye-whitness!)

• Physical examination

• Neurological examination

• Lab tests
  • Electrolytes (Na+, K+)? Hepatic function? Renal function?

• Neuroimaging: brain (CT)/MRI

• EEG

• Cardiology (syncope? arrhythmias?)

• Psychiatry (psychogenic non-epileptic seizures)
NEUROIMAGING (CT/MRI)
Neuroimaging methods (brain CT/MR)

The **first epileptic seizure** of a person (at the ER):

- **brain CT**
  - intracranial tumor
  - sinus thrombosis
  - stroke (hemorrhagic or ischemic)
  - subarachnoid hemorrhage
  - subdural/epidural haematoma
  - cerebral contusion
  - abscess

- **brain MRI**
  - epileptogenic brain lesions:
    - mesial temporal sclerosis / hippocampal sclerosis
    - focal cortical dysplasia
    - schizencephaly
    - heterotopias
    - polymicrogyria
Hippocampal sclerosis
Shizencephaly („split brain“)

Shizencephaly („split brain“): abnormal clefts lined with grey matter (uni/bilateral)
Focal cortical dysplasias
Grey matter heterotopias

Periventricular Nodular Heterotopia
Lissencephaly („smooth brain”, agyria)
EEG DIAGNOSTICS
Epilepsy: EEG diagnostics

Looking for **epileptic discharges** (e.g., spike, slow waves)

Routine scalp-EEG:
• interictal scalp-EEG with provocation tests (30 min) (hyperventilation, photostimulation)

- Sensitivity of the scalp-EEG is low (61%)
- Specificity of the scalp-EEG is low (71%)

Improving sensitivity:
• with registration during sleep
• repeated EEGs
• provocation EEGs
• using invasive (intracranial) electrodes

Interictal vs. Ictal EEG recordings

"Gold standard": long-term video-EEG monitoring
EEG scalp-electrodes
EEG Records in Epilepsy

A: Normal
Tonic-clonic seizure
1: normal
2: tonic phase
3: clonic phase
4: postconvulsive coma

B: Generalised seizure (grand mal)
Tonic-clonic type

C: Absence seizure
With sudden brief episodes of 3/s Spike & wave discharge

D: Partial seizure
Synchronous abnormal discharge in LF & LT lobes
DIFFERENTIAL DIAGNOSTICS
Seizures: Differential diagnostics

**Transient symptoms:**

- **Focal:**
  - motor
    - e.g., convulsions/jerks; clonic, tonic, myoclonic, atonic
  - non-motor
    - sensory, autonomic, cognitive

- **Generalised:**
  - motor or non-motor

- With or without loss of **consciousness** or impaired awareness

**Seizure-like conditions:**

- syncope (convulsive syncope; vasovagal syncope)
- hypoglycaemia
- hypocalcaemia (tetania)
- transient ischemic attack (TIA)
- transient global amnesia
- migraine with aura attack („migralepsy“)
- parasomnias
- involuntary movements (e.g., dystonias, tremors)
- panic attack
- psychogenic non-epileptic seizures

- epilepsy
EPILEPSY: SUMMARY

➢ Epilepsy is a seizure disorder with unclear pathomechanism
➢ Cortical hyperexcitable state
➢ Seizure symptoms are variable: motor or non-motor
➢ Classification:  ● Primary / Secondary
               ● Focal / Generalized
➢ Diagnostic tools: EEG (long-term video-EEG monitoring) & brain MRI
➢ For differential diagnostics: cardiology, psychiatry
To be continued...

NEXT WEEK
THANK YOU FOR YOUR ATTENTION
Questions
Epilepsy – Part II. Sleep disturbances

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Scheme of the lecture

• Treatment of epilepsy
• Status epilepticus
• Sleep disturbances
EPILEPSY: TREATMENT
Treatment of epilepsy

- **Pharmacological therapy:**
  - Antiepileptics/Anticonvulsants (AEDs)
    - Monotherapy
    - Polytherapy/Add-on therapy

- **Non-pharmacological therapy:**
  - in pharmacoresistant/drug refractory epilepsies:
    - Neuromodulation
      - vagus nerve stimulation
      - deep brain stimulation (targets: anterior or centromedian nucleus of the thalamus, hippocampus formation)
    - Surgical treatment
      - ablative procedures: lesionectomy, temporal lobe resection, callosotomy, etc.
    - Ketogenic diet („ketosis“) - a high-fat, adequate-protein, low-carbohydrate diet
AED generations
### AEDs – generic names

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acetazolamide</td>
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<tr>
<td>2.</td>
<td>Briviracetam</td>
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<td>3.</td>
<td>Carbamazepine</td>
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<td>4.</td>
<td>Clobazam</td>
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<tr>
<td>5.</td>
<td>Clonazepam</td>
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<td>6.</td>
<td>Eslicarbazepine acetate</td>
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<td>7.</td>
<td>Ethosuximide</td>
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<td>8.</td>
<td>Felbamate</td>
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<td>9.</td>
<td>Gabapentin</td>
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<td>10.</td>
<td>Lacosamide</td>
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<td>11.</td>
<td>Lamotrigine</td>
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<td>12.</td>
<td>Levetiracetam</td>
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<td>13.</td>
<td>Nitrazepam</td>
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<td>14.</td>
<td>Oxcarbazepine</td>
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<tr>
<td>15.</td>
<td>Perampanel</td>
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<td>16.</td>
<td>Piracetam</td>
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<td>17.</td>
<td>Phenobarbital</td>
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<td>18.</td>
<td>Phenytoin</td>
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<td>19.</td>
<td>Pregabalin</td>
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<td>20.</td>
<td>Primidone</td>
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<td>21.</td>
<td>Retigabine</td>
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<td>22.</td>
<td>Rufinamide</td>
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<td>23.</td>
<td>Sodium valproate</td>
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<td>24.</td>
<td>Stiripentol</td>
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<td>25.</td>
<td>Tiagabine</td>
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<td>26.</td>
<td>Topiramate</td>
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<td>27.</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>28.</td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>

[https://www.epilepsysociety.org.uk](https://www.epilepsysociety.org.uk)
Pharmacotherapy of epilepsy

The main aim of the treatment is:
Early and sustained seizure-free state
Good quality of life

Antiepileptics (AEDs) as drugs:
- Effectiveness
- Safety (adverse events): skin rash, hepatic, hematological (cytopenia), idiosyncrasia, teratogenicity (e.g. VPA)
- Tolerability
- CNS effects: like sedation, drowsiness, dizziness, etc.
- Pharmacokinetic properties (AMDE):
  absorption, protein binding, metabolism (CYP inducers/inhibitors), distribution, excretion
Mode of actions of AEDs

• *via* ionchannels
  • sodium (na)-ionchannel
  • calcium (ca)-ionchannel
  • potassium (k)-ionchannel

• *via* neurotransmission
  • to increase the inhibitory effects
    • GABAergic effect
  • to decrease the excitatory effects
    • anti-Glutamatergic effect
# Mode of actions of AEDs

## Modulation of ion channels

<table>
<thead>
<tr>
<th>Ion Channel Type</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ ion channel</td>
<td>PHENYTOIN, CARBAMAZEPINE, LAMOTRIGINE, LACOSAMIDE</td>
</tr>
</tbody>
</table>
| Ca²⁺ ion channel | P/Q type: GABAPENTIN, PREGABALIN  
|                  | T-type: ETHOSUXIMIDE  
|                  | K⁺ ion channel: RETIGABINE |

## Inhibitory neurotransmission (GABA-mediated effects)

- GABA-A receptor activation: BENZODIAZEPINES  
- GABA transporter inhibition: TIAGABIN  
- GABA transaminase inhibition: VIGABATRIN

## Stimulatory neurotransmission

- FELBAMATE  
- LEVETIRACETAM (SV2A)  
- TOPIRAMATE  
- VALPROATE  
- ZONISAMIDE

## Complex or special mode of action
First choice AED monotherapy

for **Focal** epilepsies:

- carbamazepine/oxcarbazepine
- levetiracetam
- phenytoin
- zonisamide

for **Generalized** epilepsies:

- valproic acid
- ethosuximide (*absence epilepsy*)
- lamotrigine
- levetiracetam (*myoclonus epilepsy*)
**ILAE guideline: Focal epilepsy**

(initial monotherapy)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBAMAZEPINE, LEVERTIRACETAM, PHENYTOIN, ZONISAMIDE</td>
<td>(level A)</td>
</tr>
<tr>
<td>VALPROIC ACID</td>
<td>(level B)</td>
</tr>
<tr>
<td>GABAPENTIN, LAMOTRIGINE, OXCARBAZEPINE, TOPIRAMATE, VIGABATRIN</td>
<td>(level C)</td>
</tr>
<tr>
<td>CLONAZEPAM, PRIMIDON</td>
<td>(level D)</td>
</tr>
</tbody>
</table>
**ILAE guideline: Generalized epilepsy (initial monotherapy)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>---</td>
</tr>
<tr>
<td>B</td>
<td>CARBAMAZEPINE/OXCARBAZEPINE, LAMOTRIGINE, PHENYTOIN, TOPIRMATE, VALPROIC ACID</td>
</tr>
<tr>
<td>C</td>
<td>GABAPENTIN, LEVETIRACETAM, VIGABATRIN</td>
</tr>
<tr>
<td>D</td>
<td>---</td>
</tr>
</tbody>
</table>
**Therapeutic recommendation**

<table>
<thead>
<tr>
<th>First choice AEDs</th>
<th>Second choice AEDs</th>
<th>In pharmacoresistant cases</th>
</tr>
</thead>
</table>
| **Focal epilepsy:**  
  - carbamazepine  
  - valproic acid  
| • carbamazepine  
  • oxcarbazepine  
  • lamotrigine  
  • levetiracetam  
  • phenytoin  
  • topiramate  
  • valproic acid  
  • zonisamide  
  • clobasam | • acetazolamide  
  • clonazepam  
  • felbamate  
  • gabapentin  
  • lacosamide  
  • primidone  
  • retigabine  
  • sulthione  
  • tiagabine  
  • vigabatrin |
| **Generalized epilepsy:**  
  - valproic acid  
  - (lamotrigine) | | |
Drug-resistant epilepsy

It is estimated that between **6-69% (median: 30%)** of epileptic patients **fail to** respond to standard medical and surgical **therapies** and continue to experience debilitating **refractory seizures**.

These patients are classified as having **drug-resistant epilepsy**.

**Definition:**
A **failure** of adequate trials of **2** tolerated, appropriately chosen and used **AED schedules** (whether as monotherapy or in combination) to achieve sustained seizure freedom.
**Epilepsy surgery**

A candidate for epilepsy surgery:
- must have **not** attained acceptable *seizure control* with sufficient trials of *AEDs* and
- must have a reasonable *chance of benefiting* from surgery

**Drug-resistant epilepsy + Focal brain (epileptogenic) lesion → evaluation for potential epilepsy surgery**
STATUS EPILEPTICUS
Status epilepticus (SE)

**Definition**: a medical and neurological emergency with significant potential morbidity and mortality

**Status epilepticus (SE)** is an epileptic seizure longer than 5 min or more.

Management of SE is aimed at:

1. *stabilization* and avoidance of secondary injury
2. *rapid* control of seizures
3. *rapid* identification/diagnosis
4. *rapid* treatment of the etiology of SE
Classification of status epilepticus

Axis 1: Semiology

different forms of SE:
- with or without prominent motor symptoms
- the degree (qualitative or quantitative) of impaired consciousness
- currently indeterminate conditions (such as acute confusional states with epileptiform EEG patterns)

Axis 2: Etiology

known (symptomatic) and unknown (cryptogenic) causes

Axis 3: EEG correlates

name of EEG pattern, morphology, location, time-related features, modulation, effect of intervention (medication)

Axis 4: Age groups

neonatal (0 to 30 days)
infancy (1 month to 2 years)
childhood (2 to 12 years)
adolescence and adulthood (12 to 59 years)
elderly (>60 years)
Nota bene!

At least half (50%) of the patients with SE do not have epilepsy (or specific epilepsy syndromes), they have SE due to acute or chronic central nervous system (CNS) or systemic (not-CNS) illness.
# Forms of status epilepticus

<table>
<thead>
<tr>
<th></th>
<th>Motor/Convulsive</th>
<th>Non-motor (NCSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generalized (GTCS)</td>
<td>Generalized (e.g. absence)</td>
</tr>
<tr>
<td></td>
<td>Focal</td>
<td>Focal</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>Normal consciousness</td>
<td>Impaired consciousness</td>
</tr>
<tr>
<td></td>
<td>(Simplex partial seizures)</td>
<td>(Complex partial seizures)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impaired consciousness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Simplex partial seizures)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Complex partial seizures)</td>
</tr>
</tbody>
</table>
Status epilepticus – common etiology

1. Low AED levels - 35%
2. Stroke, including haemorrhagic - 20%
3. Alcohol withdrawal - 15%
4. Anoxic brain injury - 15%
5. Metabolic disturbances - 15%
6. Remote brain injury/ cong. malformations - 20%
7. Infections - 5%
8. Brain neoplasms - 5%
9. Idiopathic - 5%
# Treatment of status epilepticus

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Lorazepam</td>
<td>Class I</td>
<td>Level A</td>
</tr>
<tr>
<td>2 Midazolam (IM)</td>
<td>Class I</td>
<td>Level A</td>
</tr>
<tr>
<td>3 Diazepam</td>
<td>Class IIa</td>
<td>Level A</td>
</tr>
<tr>
<td>4 Phenytoin/Fosphenytoin</td>
<td>Class IIb</td>
<td>Level A</td>
</tr>
<tr>
<td>5 Phenobarbital</td>
<td>Class IIb</td>
<td>Level A</td>
</tr>
<tr>
<td>6 Valproate sodium</td>
<td>Class IIb</td>
<td>Level A</td>
</tr>
<tr>
<td>7 Levetiracetam</td>
<td>Class IIb</td>
<td>Level C</td>
</tr>
<tr>
<td><strong>Second-line therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Class IIa</td>
<td>Level A</td>
</tr>
<tr>
<td>Phenytoin/Fosphenytoin</td>
<td>Class IIb</td>
<td>Level B</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Class IIb</td>
<td>Level B</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Class IIb</td>
<td>Level C</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class IIb</td>
<td>Level C</td>
</tr>
</tbody>
</table>
Neurology Review

Status Epilepticus

- Unremitting or back-to-back Sz for > 5 minutes
- Convulsive or Non-Convulsive Status
- Start Rx at 5 to 10 minutes
  - Benzodiazepine Therapy (Lorazepam or Diazepam)
  - AED Therapy (Phenytoin or Phenobarbital)
- Outcome depends on etiology
  - Remote symptomatic and neurodegenerative etiologies worse
  - Acute Symptomatic needs to treat the underlying cause and the seizure
  - Good prognosis for idiopathic etiology
EPILEPSY: SUMMARY

- Treatment of epilepsy is based on pharmacotherapy
- Antiepileptic drugs (mono/polytherapy)
- The aim of the treatment: sustained seizure-free
- Drug-resistant epilepsies
- Status epilepticus – to recognize it and start to treat it immediately
- Long-term follow-up of the epileptic patients
SLEEP DISTURBANCES
Scheme of the lecture
Sleep disorders
• Epidemiology
• Definition
• Classification
• Diagnostics
• Treatment
SLEEP DISORDERS: Epidemiology

40 million Americans are afflicted with chronic disorders of sleep and wakefulness, which interfere with work, driving, and social activities.

Sleep disorders cause 38,000 cardiovascular deaths/year and cost over $16 billion annually (in the USA).

Indirect costs of accidents, property destruction, litigation, hospitalization, and death add another $50 to $100 billion.

Major categories of sleep disorders:
- dyssomnias; parasomnias; sleep disorders associated with mental, neurologic, or other medical disorders; and proposed sleep disorders

The most common sleep disorders are:
- insomnia, sleep apnea, restless legs syndrome, and narcolepsy
Sleep disorders: are a group of conditions that affect the ability to sleep well on a regular basis. They can be caused by a health problem or stress. General symptoms of sleep disorders include:

- difficulty falling or staying asleep
- daytime fatigue
- strong urge to take naps during the day
- irritability or anxiety
- lack of concentration
- depression
Classification

- Substance/Medication induced sleep disorder
- Insomnia Disorder
- Hyper-somnolence Disorder
- Narcolepsy
- Breathing-related sleep disorders
- Circadian Rhythm sleep-wake disorders
- Non-REM sleep arousal disorders
- Nightmare disorder
- REM sleep behavior disorder
- Restless Leg Syndrome
SLEEP DISORDERS: Diagnostics

- Polysomnography
- EEG
- Brain MRI
- Cardiology
- Pulmonology
- Psychiatry
- Genetic blood testing (e.g., for narcolepsy)
POLYSOMNOGRAPHY
INSOMNIA

- inability to fall asleep or to remain asleep

It can be caused by: jet lag, stress and anxiety, pain, hormonal disturbances, digestive or respiratory problems

Influencing quality of life:
- depression
- difficulty concentrating
- irritability
- weight gain
- impaired work or school performance

Types:
- Chronic  (for at least one month)
- Intermittent  (occurs periodically)
- Transient  (a few nights at a time)
SLEEP APNEA: pauses in breathing during sleep

<table>
<thead>
<tr>
<th>Definition of Sleep-Related Breathing Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea</td>
</tr>
<tr>
<td>Cessation of airflow for at least 10 seconds or more</td>
</tr>
<tr>
<td>Hypopnea</td>
</tr>
<tr>
<td>Reduction of airflow with resultant oxygen desaturation of ≥4%</td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
</tr>
<tr>
<td>Average frequency of apnea and hypopnea events per hour of sleep</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>AHI of ≥15 or ≥5 associated symptoms such as excessive daytime sleepiness, impaired cognition, mood disorders, insomnia, hypertension, heart disease, or history of stroke</td>
</tr>
<tr>
<td>Central sleep apnea</td>
</tr>
<tr>
<td>AHI of ≥5 or ≥50% of the respiratory events occurring without any inspiratory effort—associated with symptoms of either excessive daytime sleepiness or disrupted sleep</td>
</tr>
</tbody>
</table>

Note: It is the presence of inspiratory effort during apneas and hypopneas that distinguishes predominantly obstructive sleep apnea from central sleep apnea.

Abbreviation: AHI, apnea-hypopnea index.

Reprinted with permission from SLACK [Khawaja et al.34].
PARASOMNIAS: 
abnormal *movements* and *behaviors* during sleep

- sleepwalking
- sleep talking
- groaning
- nightmares
- bedwetting (*enuresis nocturna*)
- teeth grinding or jaw clenching (*bruxism*)
RESTLESS LEGS SYNDROME (RLS)

- an overwhelming need to move the legs (arms)
  - accompanied by a tingling sensation in the legs/arms

- RLS is associated with:
  - ADHD (Attention Deficit Hyperactivity Disorder)
  - Parkinson’s disease

- Epidemiology:
  - 2.5–15% of the American population (women > men)

- Pathomechanism: unknown (idiopathic)
  - iron/Mg/folate deficiency, autoimmune or thyroid disorders, certain drugs
  - familial (inherited in an autosomal dominant fashion with variable penetrance) – 60%

- Therapy: dopamin-receptor agonists (e.g., pramipexole), gabapentin enacarbil, opioids
RESTLESS LEGS SYNDROME (RLS)

NIH criteria (2003):

- An urge to move the limbs (with or without sensations)
- Improvement with activity
- Worsening at rest
- Worsening in the evening or night
NARCOLEPSY: a decreased ability to regulate sleep-wake cycles

- Prevalence: 0.2 – 600/100.000 people

- Characterized by “sleep attacks” that occur during the day
  - suddenly feel extremely tired and fall asleep without warning
  - periods of excessive daytime sleepiness (sec to min)
  - may occur at any time

- Cataplexy / Sleep paralysis
  - episodes of sudden loss of muscle strength (cca. 70%)
  - cataplexy may be mistaken for seizures

- Pathomechanism: is not clear
  - family history (10%)
  - low levels of the neuropeptide orexin

- Treatment:
  - modafinil, sodium oxybate, methylphenidate
  - tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) – for cataplexy

Jean-Baptiste-Édouard Gélineau (1880)
Narcolepsy: "numbness" and "attack" (Greek)

(Movie: Due Date, 2010)
SLEEP DISORDERS: Treatment

- **Combination therapy:**
  - medical treatments + psychotherapy + lifestyle changes (sleep hygiene)

- Psychotherapy
  - Behavioral therapy
    - cognitive behavioral therapy (CBT)

- Pharmacotherapy
  - sleeping pills (BDZ or Z-drugs)
  - melatonin supplements
  - allergy or cold medication

- Breathing device (CPAP) or surgery (for sleep apnea)
  - CPAP: Continuous positive airway pressure

- Dental guard (for teeth grinding/bruxism)
SLEEP DISTURBANCES: SUMMARY

- Frequent
- Quality of life
- Comorbidity (depression, chronic pain syndrome, etc.)
- Different types of sleep disorders
- Warning: Obstructive Sleep Apnea Syndrome (OSAS) is a vascular risk factor
  - it needs treatment (CPAP)
- Complex treatment and management
THANK YOU FOR YOUR ATTENTION
Questions?