Antiepileptic drugs
Epilepsy
EPILEPSY

CNS disorders characterized by recurrent, sudden, transient episodes of abnormal motor (convulsions), sensory, vegetative or psychic phenomena (seizures).

Seizures are associated with high amplitude EEG discharges, and can be associated with loss of consciousness.

It is estimated that epilepsies affect 1% of the global population.
DEFINITION (ILAE 2005)

An **epileptic seizure** is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. **Epilepsy** is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition.
CLASSIFICATION of EPILEPSY

Seizures originate from cortical sites of one or both hemispheres

- Partial epilepsy (60%)
- Generalised epilepsy (40%)
1. Idiopathic: not attributable to obvious causes

2. Symptomatic: existence of a primary cause

Vascular damage
Traumas
Congenital malformations
Metabolic disorders
Neoplasia
Infections
Drugs
Hyperthermia in pediatric age

Ictus (50/100.000 pazienti)
Diffusion of epilepsy
Diagnosis
EEG in epilepsy

A Normal

B Generalised seizure (grand mal) — tonic-clonic type

C Generalised seizure (petit mal) — absence seizure type

D Partial seizure
Per misurare il flusso ematico regionale nell’encefalo può essere usata la tomografia computerizzata a emissione di fotoni singoli (SPECT). L’immagine mostra un aumento del flusso nel lobo temporale sinistro associato con l’insorgenza di un attacco nella stessa area.
Genetics of epilepsy

- Epileptic syndromes caused by a single mutant gene, familiar (example: generalized epilepsy with febrile seizures, GEFS+) or de novo (example: Dravet).
- Epileptic syndromes caused by two or more predisposing genes (example: infantile myoclonic epilepsy).
- Mutations induced in rodents that associate with epilepsy (example: GABA$_A$ receptor subunits).
- Mutations induced in rodents that associate with reduced susceptibility to seizures (example: TrkB).
- Epilepsy due to spontaneous mutations in rodents (example: Ca$^{2+}$ channels).
• Channels (Na\(^+\), K\(^+\), Ca\(^{2+}\)) ➔ alterations in the intrinsic properties of the neuron.
• Molecular mechanisms of neurotransmitter release (synapsins, Sv2A) ➔ unbalance between excitatory and inhibitory signals.
• GABAergic transmission (loss of function) ➔ alterations in GABA synthesis, release, receptors.
• Glutamatergic transmission (gain of function) ➔ alterations in glutamate receptors or reuptake.
• Other receptors: neuronal nicotinic receptor \(\alpha4\) subunit; 5HT\(_{2C}\) receptors.
Pharmacology
History

ante-1857  Folklore (epilepsy: taking possession; sacré disease)

1857  Bromide (K)

1912  Fenobarbital

1938  Fenitoine

1951  Ethosuximide

60 /70th  Carbamazepine, Benzodiazepine, Valproate

90th  New antiepileptics:

  Vigabatrine, Lamotrigine, Gabapentine, Felbamate, Oxcarbazepine
<table>
<thead>
<tr>
<th>SEIZURE TYPE</th>
<th>FEATURES</th>
<th>CONVENTIONAL ANTISEIZURE DRUGS</th>
<th>RECENTLY DEVELOPED ANTISEIZURE DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARTIAL SEIZURES:</strong></td>
<td>Diverse manifestations determined by the region of cortex activated by seizure (e.g., if motor cortex representing left thumb, clonic jerking of left thumb results; if somatosensory cortex representing left thumb, paresthesia of left thumb results), lasting approximating 20 to 60 seconds. <strong>Key feature is preservation of consciousness.</strong></td>
<td>Carbamazepine, phenytoin, valproate</td>
<td>Gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, zonisamide</td>
</tr>
<tr>
<td>Simple partial</td>
<td>Impaired consciousness lasting 30 seconds to two minutes, often associated with purposeless movements such as lip smacking or hand wringing.</td>
<td>Carbamazepine, phenytoin, valproate</td>
<td>Gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, zonisamide</td>
</tr>
<tr>
<td>Complex partial</td>
<td>Simple or complex partial seizure evolves into a tonic-clonic seizure with loss of consciousness and sustained contractions (tonic) of muscles throughout the body followed by periods of muscle contraction alternating with periods of relaxation (clonic), typically lasting 1 to 2 minutes.</td>
<td>Carbamazepine, phenobarbital, phenytoin, primidone, valproate</td>
<td>Gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, zonisamide</td>
</tr>
</tbody>
</table>
GENERALIZED SEIZURES:

Absence seizure
Abrupt onset of impaired consciousness associated with staring and cessation of ongoing activities typically lasting less than 30 seconds.

Ethosuximide, valproate

Lamotrigine

Myoclonic seizure
A brief (perhaps a second), shocklike contraction of muscles which may be restricted to part of one extremity or may be generalized.

Valproate

Lamotrigine, topiramate

Tonic-clonic seizure
As described above for partial with secondarily generalized tonic-clonic seizures except that it is not preceded by a partial seizure.

Carbamazepine, phenobarbital, phenytoin, primidone, valproate

Lamotrigine, topiramate
Therapeutic strategies

- Epilessia di nuova diagnosi
- Farmaco di prima scelta 47% → Senza attacchi
- Farmaco di seconda scelta 13% → Senza attacchi
- Associazione razionale di due farmaci 40%
Meccanism of action
Molecular basis of Epilepsy (1)

GABA

Glutamate
First target: sodium channels
Some anti-epileptic drug (AED) prolong the inactivation period of sodium channels, reducing the ability of neurons to discharge at high frequencies.
Many AED (PHENYTOIN, CARBAMAZEPINE, OXCARBAMAZEPINE, LAMOTRIGINE, VALPROATE, FELBAMATE, TOPIRAMATE, ZONISAMIDE, LACOSAMIDE, RUFINAMIDE, ESLICARBAZEPINE) prolong the inactivation period of sodium channels, reducing the ability of neurons to discharge at high frequencies.
Second target: GABA
GABAergic system

Fig. 2. Possible sites of interaction of antiepileptic drugs on GABA-mediated transmission. GABA is formed from glutamate by the action of glutamic acid decarboxylase (GAD), and can be metabolized by GABA aminotransferase (GABA-T) to form succinic acid semialdehyde (SSA). The GABA_A receptor is associated with an ion channel permeable to Cl⁻; GABA increases the probability of ion channel opening, which leads to an elevation of intracellular Cl⁻ levels and hyperpolarization. Barbiturates and benzodiazepines act via associated modulatory sites to potentiate the effect of GABA on Cl⁻ conductance.
- **BARBITURATES** and **BENZODIAZEPINES** increase GABA signaling on \( \text{GABA}_A \) receptors.
- **TIAGABINE** inhibits GABA reuptake in neurons and glia.
- **VIGABATRIN** and valproate inhibit GABA transaminase.
- **STIRIPENTOL** increases GABA signaling on \( \text{GABA}_A \) receptors and also increases synaptic levels of GABA by inhibiting reuptake and GABA transaminase.
Third target: glutamatergic synapses
With different mechanisms, some AED reduce the glutamate signal.
• **GABAPENTIN** and **PREGABALIN** inhibit glutamate release (via interaction with the $\alpha2\delta$ subunit of L-type Ca$^{2+}$ channels and inhibition of Ca$^{2+}$ currents?), without effects on GABA receptors.

• **FELBAMATE** inhibits excitatory signals (and also increases GABA-mediated inhibitory responses).

• **TOPIRAMATE** reduces glutamate receptor activation (and also prolongs the inactivation period of sodium channels, and potentiates GABAergic activity).

• **PERAMPANEL** is a non-competitive and selective AMPA antagonist.
Fourth target: T-type calcium channels
AED that are active on absence seizures (ETHOSUXIMIDE, VALPROATE) reduce T-type Ca\(^{2+}\) currents.
Fifth target: synaptic transmission
LEVETIRACETAM binds synaptic vesicle 2° (SV2A), a protein ubiquitously found in brain synaptic vesicles.

- The function of SV2A and the mechanism of action of levetiracetam are uncertain.
- SV2A KO mice have reduced release of both GABA and glutamate.
Side effects and negative interactions
Mechanism of antiepileptic drugs
+ side effects

- **Phenytoin:**
  - acts mainly by use-dependent block of sodium channels
  - effective in many forms of epilepsy, but not absence seizures
  - metabolism shows saturation kinetics; therefore, plasma concentration can vary widely and monitoring is needed
  - drug interactions are common
  - main unwanted effects are confusion, gum hyperplasia, skin rashes, anaemia, teratogenesis
  - widely used in treatment of epilepsy; also used as antidyssrhythmic agent.

- **Carbamazepine:**
  - derivative of tricyclic antidepressants
  - similar profile of that of phenytoin, but with fewer unwanted effects
  - effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor epilepsy; also useful in trigeminal neuralgia
  - strong enzyme-inducing agent; therefore, many drug interactions
  - low incidence of unwanted effects; principally sedation, ataxia, mental disturbances, water retention.

- **Valproate:**
  - chemically unrelated to other antiepileptic drugs
  - mechanism of action not clear; weak inhibition of GABA transaminase; some effect on sodium channels
  - related few unwanted effects: baldness, teratogenicity, liver damage (rare, but serious).

- **Ethosuximide:**
  - the main drug used to treat absence seizures, may exacerbate other forms
  - acts by blocking T-type calcium channels
  - relatively few unwanted effects, mainly nausea and anorexia.

- **Secondary drugs include:**
  - phenobarbital: highly sedative
  - various benzodiazepines (e.g. clonazepam); diazepam used in treating status epilepticus.
Non linear effect of *Phenytoin* on plasma concentration

Slow absorption
It binds plasma proteins (80-90%)
(salicylates, phenylbutazone, valproate)

Inactive metabolites
<5% excretion unchanged
T ½ 24 hours

Drowsiness and lethargy
Further idantoinic drugs

**Fosphenytoin:**
Phenytoin pro-drug
Intramuscularly, e.v.

**Mephetoine:**
Lower incidence of:
ataxia, gingival hyperplasia
Gastrointestinal effects
Increased incidence of severe ematologic reactions and hepatitis
Farmaci che stimolano il metabolismo della fenitoina

Carbamazepina

Fenitoina + Metabolita inattivo

Fenitoina − Metabolita

Farmaci che inibiscono il metabolismo della fenitoina

- Cloramfenicolo: Antibiotic
- Dicumarolo: Anticoagulant
- Cimetidina: Antiulcer
- Sulfonamide: Antibacterial
- Isoniazide: Anti-tuberculosis

Phenytoine induces P-450
Mechanism of antiepileptic drugs
+ side effects

- **Phenytoin:**
  - acts mainly by use-dependent block of sodium channels
  - effective in many forms of epilepsy, but not absence seizures
  - metabolism shows saturation kinetics; therefore, plasma concentration can vary widely and monitoring is needed
  - drug interactions are common
  - main unwanted effects are confusion, gum hyperplasia, skin rashes, anaemia, teratogenesis
  - widely used in treatment of epilepsy; also used as antidysrhythmic agent.

- **Carbamazepine:**
  - derivative of tricyclic antidepressants
  - similar profile of that of phenytoin, but with fewer unwanted effects
  - effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor epilepsy; also useful in trigeminal neuralgia
  - strong enzyme-inducing agent; therefore, many drug interactions
  - low incidence of unwanted effects; principally sedation, ataxia, mental disturbances, water retention.

- **Valproate:**
  - chemically unrelated to other antiepileptic drugs
  - mechanism of action not clear; weak inhibition of GABA transaminase; some effect on sodium channels
  - related few unwanted effects: baldness, teratogenicity, liver damage (rare, but serious).

- **Ethosuximide:**
  - the main drug used to treat absence seizures, may exacerbate other forms
  - acts by blocking T-type calcium channels
  - relatively few unwanted effects, mainly nausea and anorexia.

- **Secondary drugs include:**
  - phenobarbital: highly sedative
  - various benzodiazepines (e.g. clonazepam); diazepam used in treating status epilepticus.
**CARBAMAZEPINE**

**Farmaci che inibiscono il metabolismo della carbamazepina**
- Cimetidina: antiulcer
- Diltiazem: Ca + blocker
- Eritromicina: Antibiotic
- Isoniazide: Anti-tuberculosis
- Propossifene: Analgesic

**CYP3A4**
- Decrease concentration of:
  - carbamazepine
  - oral contraceptives
  - benzodiazepines
  - antidepressants
  - antibiotics
  - phenytoin
  - corticosteroids
  - warfarin

Metabolite 10,11-epoxide: blood dyscrasias (leukopenia, aplastic anemia), liver toxicity
Side effects of *carbamazepine* and *oxcarbazepine*
Introduced in 1978 in the USA

Chemistry:
acts in ionized form

Action mechanisms:
GAD enhancement
GABA-T inhibition
GAT-1 inhibition
Block of Ca + and Na + channels
Activation of K + channels
Inhibits histone deacetylase
Valproic Acid

Pharmacokinetics:
- Rapid absorption
- 90% plasma protein binding
- Metabolized liver (active metabolites), does not induce P-450
- Escretion urine glucuronidate. Unchanged 3%

Side Effects
- Thrombocytopenia, platelet aggregation inhibition (bleeding), teratogenesis, liver damage
- Inhibits phenobarbital metabolism, carbamazepine, etosuccimide
Side effects of valproic acid

- Nausea
- Tremors
- Somnolence
- Hepatic insufficiency
EFFECT OF SOME ANTIEPILEPTIC DRUGS ON REPETITIVE NEURONAL DISCHARGE
Ethosuximide

Pharmacokinetics:
- Rapid absorption
- Does not bind to plasma proteins
- 75% metabolized liver (inactive metabolites), does not induce P-450
- 25% unchanged excreted

Side effects:
- It can exacerbate other forms of epilepsy
- Nausea and vomit
- Sedation, drowsiness, lethargy, dizziness, restlessness, anxiety agitation
- Leukopenia, aplastic anemia, thrombocytopenia
MOLECULAR MECHANISMS OF ANTIEPILEPTIC DRUGS: BLOCKING OF VOLTAGE-DEPENDENT CHANNELS and Ca+ CHANNELS

- High affinity for the inactivated state of the Ca+ channels

- Block with similar characteristics of use-dependence and voltage-dependence
Barbiturate
MOLECULAR MECHANISMS OF ANTIEPILEPTIC DRUGS:
GABAERICGIC NEUROTRANSMISSION

GABA
Phenobarbital and primidone

**Farmacokinetic:**
Complete not rapid absorption
75% metabolized in liver (inactive metabolites), induces P-450

Primidone: partially transformed into phenobarbital

**Side effects**
Sedation, ataxia, vertigo. With high doses, agitation and confusion
After suspending convulsive rebound attack
Bromides: increase the GABA-AR mediated currents because bromine permeates better than chloride through it

Benzodiazepines: increase the affinity of GABA for GABA-AR

Topiramate: Na channel, potentiates GABA activity, reduce activation of GluR

Barbiturates: increase the average opening time of GABA-AR

Valproic acid: stimulates GAD and inhibits GABA transaminase
Duration of action of barbiturates

- **Fenobarbital**
  - Duration: 1–2 giorni

- **Breve**
  - Duration: 3–8 ore
  - Barbiturates: Pentobarbital, Secobarbital, Amobarbital

- **Ultrabreve**
  - Duration: 20 minuti
  - Barbiturate: Tiopental
Side effects of barbiturates
Le benzodiazepine sono relativamente sicure, giacché la dose letale è più di 1000 volte più grande della dose terapeutica usuale.

<table>
<thead>
<tr>
<th></th>
<th>Rapporto = ( \frac{Dose \text{ letale}}{Dose \text{ efficace}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morfina</td>
<td></td>
</tr>
<tr>
<td>Clorpromazina</td>
<td></td>
</tr>
<tr>
<td>Fenobarbital</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
</tr>
<tr>
<td>Farmaco</td>
<td>Blocco dei Canali del Na⁺</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Fenitoina</td>
<td>+++</td>
</tr>
<tr>
<td>Carbamazepina</td>
<td>+++</td>
</tr>
<tr>
<td>Oxcarbazepina</td>
<td>+++</td>
</tr>
<tr>
<td>Fenobarbital</td>
<td>+</td>
</tr>
<tr>
<td>Etosuccimide</td>
<td>+++</td>
</tr>
<tr>
<td>Acido valproico</td>
<td>+</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td></td>
</tr>
<tr>
<td>Gabapentina</td>
<td>++ IVA, α₂δ</td>
</tr>
<tr>
<td>Lamotrigina</td>
<td>+++</td>
</tr>
<tr>
<td>Topiramato</td>
<td>++</td>
</tr>
<tr>
<td>Tiagabina</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>+</td>
</tr>
<tr>
<td>Felbamato</td>
<td>++</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>+</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td></td>
</tr>
<tr>
<td>Farmaco</td>
<td>Legame proteine (%)</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Fenitoina</td>
<td>90</td>
</tr>
<tr>
<td>Carbamazepina</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepina</td>
<td>40% (derivato mono-</td>
</tr>
<tr>
<td></td>
<td>idrossilato MHD)</td>
</tr>
<tr>
<td>Fenobarbital</td>
<td>40-60</td>
</tr>
<tr>
<td>Etosuccimide</td>
<td>0</td>
</tr>
<tr>
<td>Acido valproico</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>98 diazepam; 85</td>
</tr>
<tr>
<td></td>
<td>clonazepam 14</td>
</tr>
<tr>
<td>Gabapentina</td>
<td>0</td>
</tr>
<tr>
<td>Lamotrigina</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Main pharmacokinetic properties, indications and toxicity of antiepileptic drugs

<table>
<thead>
<tr>
<th>Farmaco</th>
<th>Legame proteine (%)</th>
<th>Emivita (ore)</th>
<th>Posologia (mg/kg/die)</th>
<th>Intervallo terapeutico (µg/ml)</th>
<th>Indicazioni</th>
<th>Tossicità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramato</td>
<td>15</td>
<td>20-30</td>
<td>3-10</td>
<td>4-10</td>
<td>Epilessie parziali e tonicocloniche generalizzate</td>
<td>Sonnolenza; irritabilità; parestesie; nefrotasie; glaucoma; depressione e psicosi</td>
</tr>
<tr>
<td>Tragabina</td>
<td>96</td>
<td>5-8</td>
<td>0.2-1</td>
<td>0.2-0.8</td>
<td>Epilessie parziali</td>
<td>Nervosismo; depressione; disorientamento</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Basso</td>
<td>24-72</td>
<td>2-10</td>
<td>20-50</td>
<td>Epilessie parziali; generalizzate tonicocloniche</td>
<td>Sonnolenza; anoressia; rashes cutanei, calcoli renali, atassia</td>
</tr>
<tr>
<td>Felbamato</td>
<td>25-35</td>
<td>20</td>
<td>30-60</td>
<td>30-100</td>
<td>Epilessie parziali; sindrome di Lennox-Gastaut</td>
<td>Anemia aplastica; epatite</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>&lt;10</td>
<td>6-8</td>
<td>7-70</td>
<td>6-20</td>
<td>Epilessie tonico-cloniche e parziali</td>
<td>Sonnolenza; astenia; vertigini; irritabilità</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>scarso</td>
<td>5-7</td>
<td>20-40</td>
<td>5-35</td>
<td>“add-on” nell’epilessie complesse parziali e secondariamente generalizzate; spasmi infantili</td>
<td>Diffetti del campo visivo, psicosi e depressione, aumento ponderale; le assenze e l’epilessie miocloniche possono peggiorare</td>
</tr>
</tbody>
</table>

Caratteristiche farmacocinetiche
## Interactions of antiepileptic drugs with the enzymatic families involved in drug metabolism

<table>
<thead>
<tr>
<th>Farmaco</th>
<th>Induzione Farmacometabolica</th>
<th>Inibizione farmacometabolica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenitoina</td>
<td>CYP2C e 3A; UGT</td>
<td>CYP</td>
</tr>
<tr>
<td>Carbamazepina</td>
<td>CYP1A2, 2C9, 2C19, e 3A4; UGT</td>
<td>—</td>
</tr>
<tr>
<td>Oxcarbazepina</td>
<td>CYP3A4</td>
<td>CYP2C19, UGT (debole)</td>
</tr>
<tr>
<td>Fenobarbitale</td>
<td>CYP1A2, 2C9, 2C19, e 3A4; UGT</td>
<td>—</td>
</tr>
<tr>
<td>Etosuccimide</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Acido valproico</td>
<td>—</td>
<td>CYP2C9, 2C19; UGT 1A4</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gabapentina</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lamotrigina</td>
<td>UGT</td>
<td>—</td>
</tr>
<tr>
<td>Topiramato</td>
<td>CYP3A4 (debole)</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Tiagabina</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Felbamato</td>
<td>CYP3A4 (debole)</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Therapeutic advantages

Therapeutic disadvantages
SPECIFIC PROBLEMS IN ANTIEPILEPTIC THERAPY

1. DRUG RESISTANCE

2. ANTICONVULSIVE THERAPY IN PREGNANCY
**Therapy during pregnancy**

1. Exposure of the fetus to phenytoin, carbamazepine, valproate, phenobarbital and other AEDs has been associated with congenital anomalies, like cleft lip, spina bifida (valproate), cardiac alterations and neural tube defects.
2. High plasmatic concentrations, or poli-therapy, increase the risk of malformation.
3. More recent drugs are not teratogenic in animals.