Antiepileptic drugs
Diffusion of epilepsy

for 100,000
less than 50
50-72.5
72.5-95
95-117.5
117.5-140
140-162.5
162.5-185
185-207.5
207.5-230
230-252.5
252.5-275
more than 275
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.
ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset
- Aware
  - Impaired Awareness

Motor Onset
- automatisms
- atonic
- clonic
- epileptic spasms
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset
- Motor
  - tonic-clonic
  - clonic
  - tonic
  - myoclonic
  - myoclonic-tonic-clonic
  - myoclonic-atonic
  - atonic
  - epileptic spasms

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset
- Motor
  - tonic-clonic
  - epileptic spasms
- Non-Motor
  - behavior arrest

Unclassified

“During these electrical firings, my visions flourish and I hallucinate indescribable visions. I have felt virtual slivers slicing my throat when I draw the air to describe them. I’m sucked down into the explosion, fumble through the chaos, and land disembodied from the intensity.”

“After I have a seizure, I get an overwhelming sense that everything I know intellectually to be in the present is distant in time and space, like the sort of sense associated with the recollection of an old memory. I have a powerful sense of anguish, pain, and loneliness.”
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
Regional blood flow during epilepsy 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.
ETIOLOGY OF EPILEPSY

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)
Epilepsy genes

- Channels ($\text{Na}^+, \text{K}^+, \text{Ca}^{2+}$) $\Rightarrow$ alterations in the intrinsic properties of the neuron.
- Molecular mechanisms of neurotransmitter release (synapsins, Sv2A) $\Rightarrow$ unbalance between excitatory and inhibitory signals.
- GABAergic transmission (*loss of function*) $\Rightarrow$ alterations in GABA synthesis, release, receptors.
- Glutamatergic transmission (*gain of function*) $\Rightarrow$ alterations in glutamate receptors or reuptake.
- Other receptors: neuronal nicotinic receptor $\alpha_4$ subunit; 5HT$_{2C}$ receptors.
Ictogenesis in lesional epilepsies
(transition from the interictal state to a seizure)

Alterations in the intrinsic properties of the neuron: channels ($\text{Na}^+$, $\text{K}^+$).

Unbalance between excitatory (glutamate) and inhibitory (GABA) signals.
Pharmacology
History

ante-1857  Folklore (epilepsy: taking possession; sacre 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple partial</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>Complex 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>Partial with secondarily generalized tonic-clonic</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
Mechanism of action of drugs
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.
Second target: K channel
Second target: **potassium channels**.

**RETIGABINE**: a *potassium channel opener* (neuronal potassium channel Kv7).

focal and tonic-clonic generalized seizures
Side effects

• Prolonged treatments: blue color of the skin (nails and lips) and alterations in retina pigments ➔ periodic eye exams (reversibility?)

• Prolonged QT interval ➔ attention to cardiopathic patients and ECG monitoring
Molecular basis of Epilepsy

GABA

Glutamate
Third 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<sub>A</sub> receptor is associated with an ion channel permeable to Cl<sup>−</sup>; GABA increases the probability of ion channel opening, which leads to an elevation of intracellular Cl<sup>−</sup> levels and hyperpolarization. Barbiturates and benzodiazepines act via associated modulatory sites to potentiate the effect of GABA on Cl<sup>−</sup> conductance.
• **BARBITURATES** and **BENZODIAZEPINES** increase GABA signaling on GABA\(_A\) receptors.
• **TIAGABINE** inhibits GABA reuptake in neurons and glia.
• **VIGABATRIN** and valproate inhibit GABA transaminase.
• **STIRIPENTOL** increases GABA signaling on GABA\(_A\) receptors and also increases synaptic levels of GABA by inhibiting reuptake and GABA transaminase.
Fourth target: glutamatergic synapses
With different mechanisms, some AED reduce the glutamate signal.
• GABAPENTIN and PREGABALIN inhibit glutamate release (via interaction with the $\alpha_2\delta$ 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.
Fifth target: T-type calcium channels
AED that are active on absence seizures (ETHOSUXIMIDE, VALPROATE) reduce T-type Ca\textsuperscript{2+} currents.
Sixth 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

**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 antidyrsrhythmic 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 $\frac{1}{2}$ 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 hematologic reactions and hepatitis
Farmaci che stimolano il metabolismo della fenitoina

*Carbamazepina*

Fenitoina

**Metabolita inattivo**

Metabolita

Farmaci che inibiscono il metabolismo della fenitoina

*Cloramfenicolo*  
*Dicumarolo*  
*Cimetidina*  
*Sulfonamide*  
*Isoniazide*

Antibiotic  
Anticoagulant  
Antiulcer  
Antibacterial  
Anti-tuberculosis

**Phenytoine induces P-450**
Mechanism of antiepileptic drugs

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  - 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
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CARBAMAZEPINE

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
Mechanism of antiepileptic drugs

+ side effects

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  - phenobarbital: highly sedative
  - various benzodiazepines (e.g. clonazepam); diazepam used in treating status epilepticus.
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*
EFFECT OF SOME ANTIEPILEPTIC DRUGS ON REPETITIVE NEURONAL DISCHARGE
• 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.

• 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).

• 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
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• 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.
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
**Indications**
- Focal and generalized seizures (50% reduction in 25% of the patients)
- Absence seizures
- In association for the Lennox-Gastaut syndrome

**Formulations**
- Oral

**Pharmacokinetics (PK)**
- Rapid and complete absorption after oral administration
- Protein binding 55%
- Metabolism: glucuronic acid conjugation
- Renal elimination; half-life 24 h

**Pharmacodynamics**
- Prolongs the inactivation period of sodium channels
- Reduces neurotransmitter release (glutamate)

**Side effects**
- Gastrointestinal: nausea, vomit
- Dizziness, ataxia, somnolence
- Serious and dangerous rash in 0.3% of adults and 1% of children (Stevens-Johnson)
Barbiturate
MOLECULAR MECHANISMS OF ANTIEPILEPTIC DRUGS: GABAERGIC NEUROTRANSMISSION

GABA

[Diagram showing GABA receptor sites with labels for Barbiturici, GABA, Bicucullina, Picrotossina, Neurosteroidi, and Benzodiazepine.]
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
Side effects of barbiturates

- POTENZIALITÀ DI TOSSICODIPENDENZA
- VERTIGINI
- SONNolenza
- TREMORI

Barbiturico
P-450
P-450

Metabolita
INDUZIONE ENZIMATICA
## MAIN MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

<table>
<thead>
<tr>
<th>Farmaco</th>
<th>Blocco dei Canali del Na⁺</th>
<th>Blocco dei Canali del Ca²⁺</th>
<th>Attivazione della Neurotrasmissione GABAergica</th>
<th>Altri Meccanismi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenitoina</td>
<td>+++</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Carbamazepina</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepina</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenobarbital</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Etosuccimide</td>
<td>+++</td>
<td></td>
<td>+ blocco GABA-T</td>
<td>blocco Na⁺/K⁺ ATPasi</td>
</tr>
<tr>
<td>Acido valproico</td>
<td>+</td>
<td>+</td>
<td></td>
<td>attivazione canali del K⁺</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td></td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentina</td>
<td>+ IVA, α₂δ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigina</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramato</td>
<td>++</td>
<td>+</td>
<td></td>
<td>antagonismo recettori AMPA</td>
</tr>
<tr>
<td>Tiagabina</td>
<td></td>
<td>+++</td>
<td>inibizione GAT-1</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
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<tr>
<td>Felbamato</td>
<td>++</td>
<td></td>
<td></td>
<td>antagonismo recettori NMDA</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>+</td>
<td></td>
<td></td>
<td>Legame al SV2A</td>
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<tr>
<td>Vigabatrin</td>
<td>+++</td>
<td></td>
<td>inibizione GABA-T</td>
<td></td>
</tr>
<tr>
<td>Farmaco</td>
<td>Legame proteine (%)</td>
<td>Emivita (ore)</td>
<td>Posologia (mg/kg/die)</td>
<td>Intervallo terapeutico (µg/ml)</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------</td>
<td>---------------</td>
<td>-----------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Fenitoina</td>
<td>90</td>
<td>24 (dose-dipendente)</td>
<td>3-5</td>
<td>10-20</td>
</tr>
<tr>
<td>Carbamazepina</td>
<td>70</td>
<td>8-26</td>
<td>10-20</td>
<td>6-12</td>
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<tr>
<td>Oxcarbazepina</td>
<td>40% (derivato mono- idrossilato MHD)</td>
<td>1-5 (oxcarbazepina) 7-20 (MHD)</td>
<td>8-13</td>
<td>15-35 (MHD)</td>
</tr>
<tr>
<td>Fenobarbital</td>
<td>40-60</td>
<td>25-140</td>
<td>1.5-3.5</td>
<td>15-40</td>
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<tr>
<td>Etosuccimide</td>
<td>0</td>
<td>30-40</td>
<td>15-25</td>
<td>40-80</td>
</tr>
<tr>
<td>Acido valproico</td>
<td>94</td>
<td>8-15</td>
<td>20-40</td>
<td>40-100</td>
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<tr>
<td>Benzodiazepine</td>
<td>98 diazepam 85 clonazepam</td>
<td>1-2 diazepam; 20-48 clonazepam 14 lorazepam</td>
<td>0,1-0,2 diazepam</td>
<td>20-70</td>
</tr>
<tr>
<td>Gabapentina</td>
<td>0</td>
<td>6-9</td>
<td>10-25</td>
<td>25-50</td>
</tr>
<tr>
<td>Lamotrigina</td>
<td>55</td>
<td>24-35</td>
<td>4-8</td>
<td>1.5-10 (concentrazione bersaglio iniziale)</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; nefrotisi; glaucoma; depressione e psicosi</td>
</tr>
<tr>
<td>Trigabina</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 tonicocloniche 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>Difetti del campo visivo, psicosi e depressione, aumento ponderale; le assenze e l’epilessie miocloniche possono peggiorare</td>
</tr>
</tbody>
</table>
## 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>
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<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>
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<tr>
<td>Etosucimide</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>
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<td>—</td>
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<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>
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<tr>
<td>Vigabatrin</td>
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</tr>
</tbody>
</table>
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.