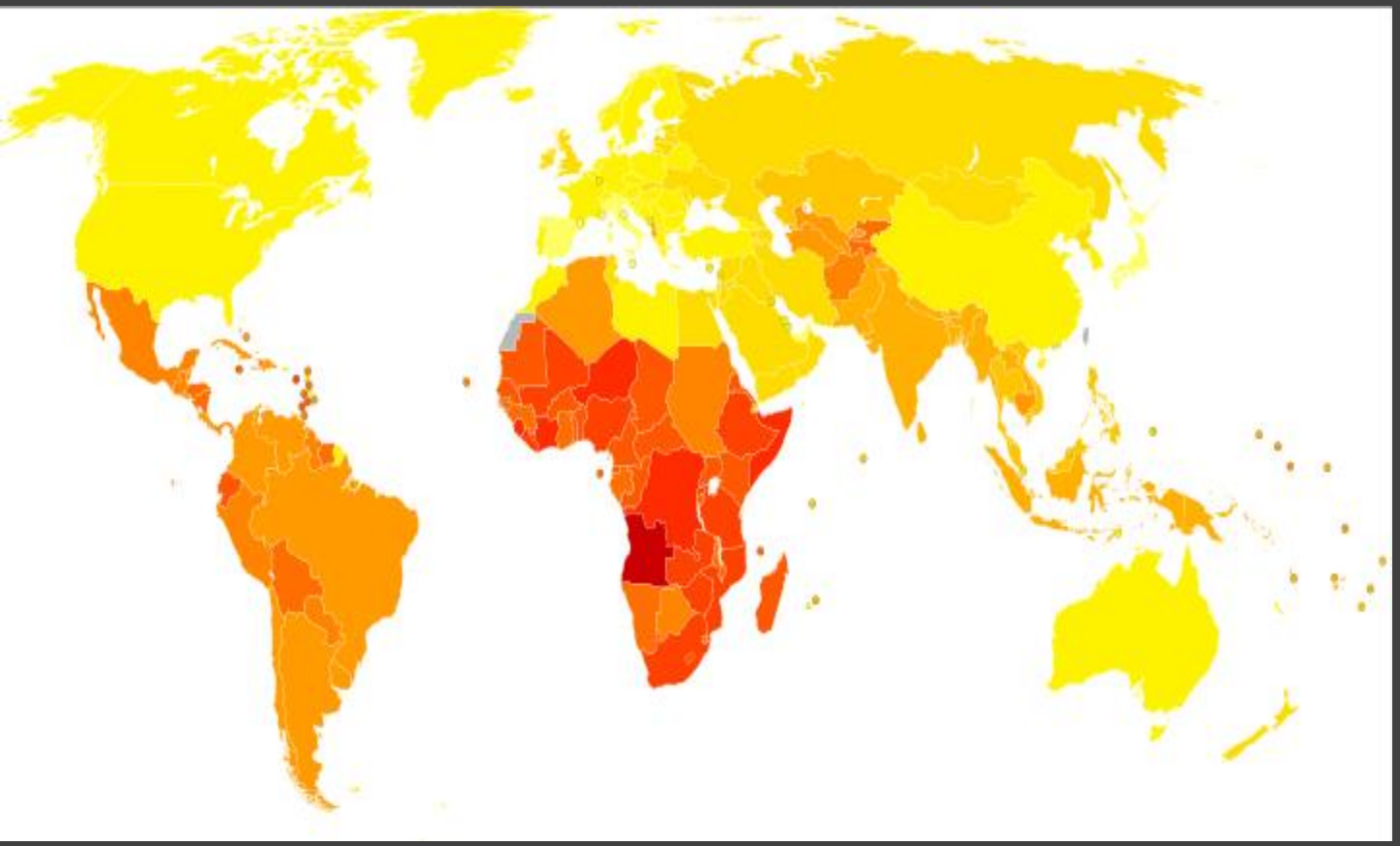
Antiepileptic drugs

Diffusion of epilepsy

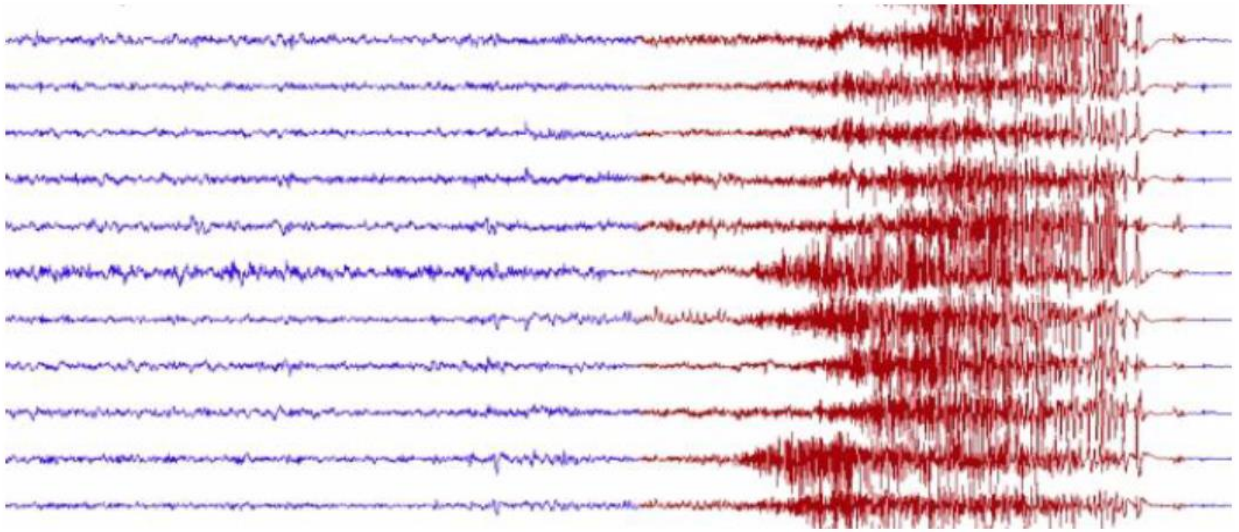


for 100.000
less than 50
50-72.5
72.5-95
95-117.5
117.5-140
140-162.5
162.5-185
185-207.5
207.5-230
230-252.5
252.5-275
more than 275

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[2]
- clonic
- epileptic spasms[2]
- 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[2]

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

Unknown Onset

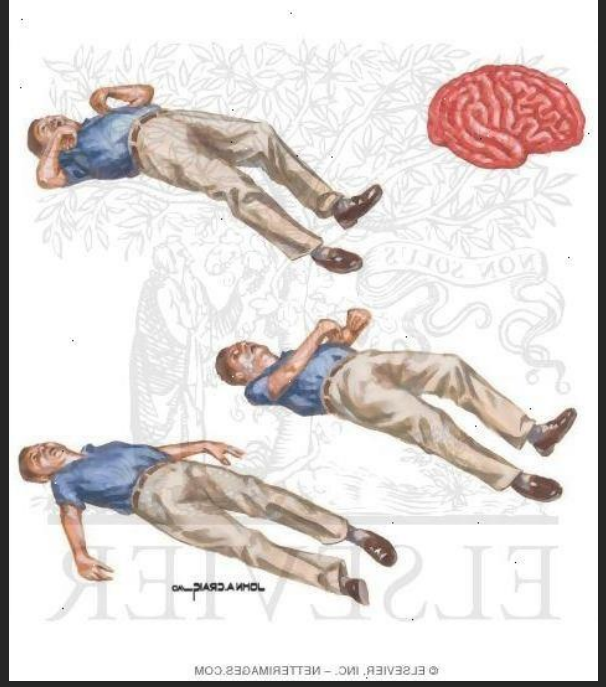
Motor
- tonic-clonic
- epileptic spasms

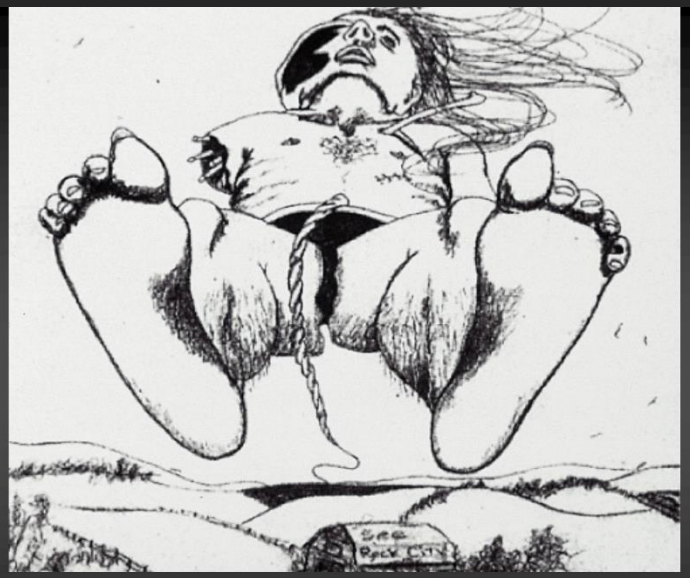
Non-Motor
- behavior arrest

Unclassified[3]

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

"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."

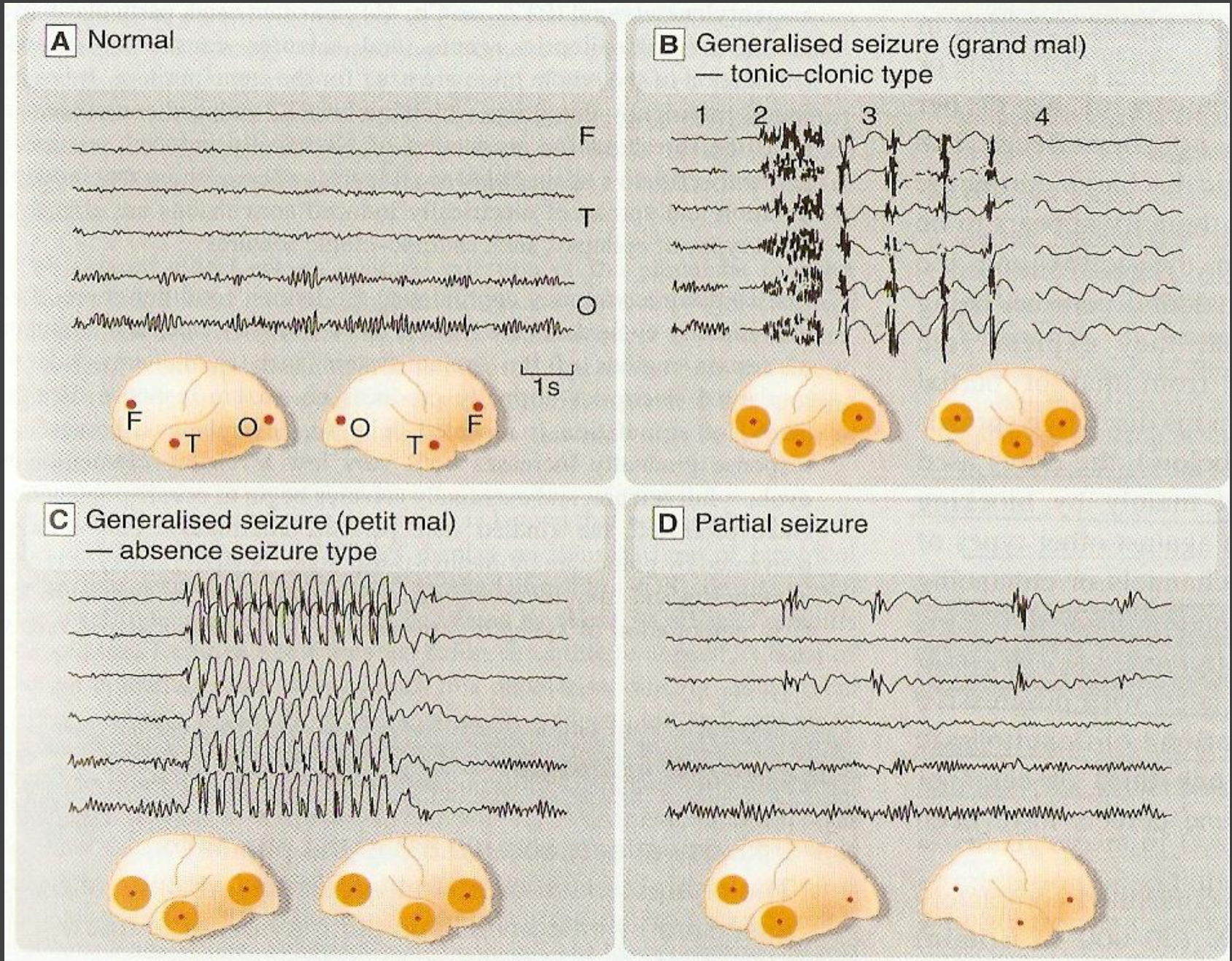




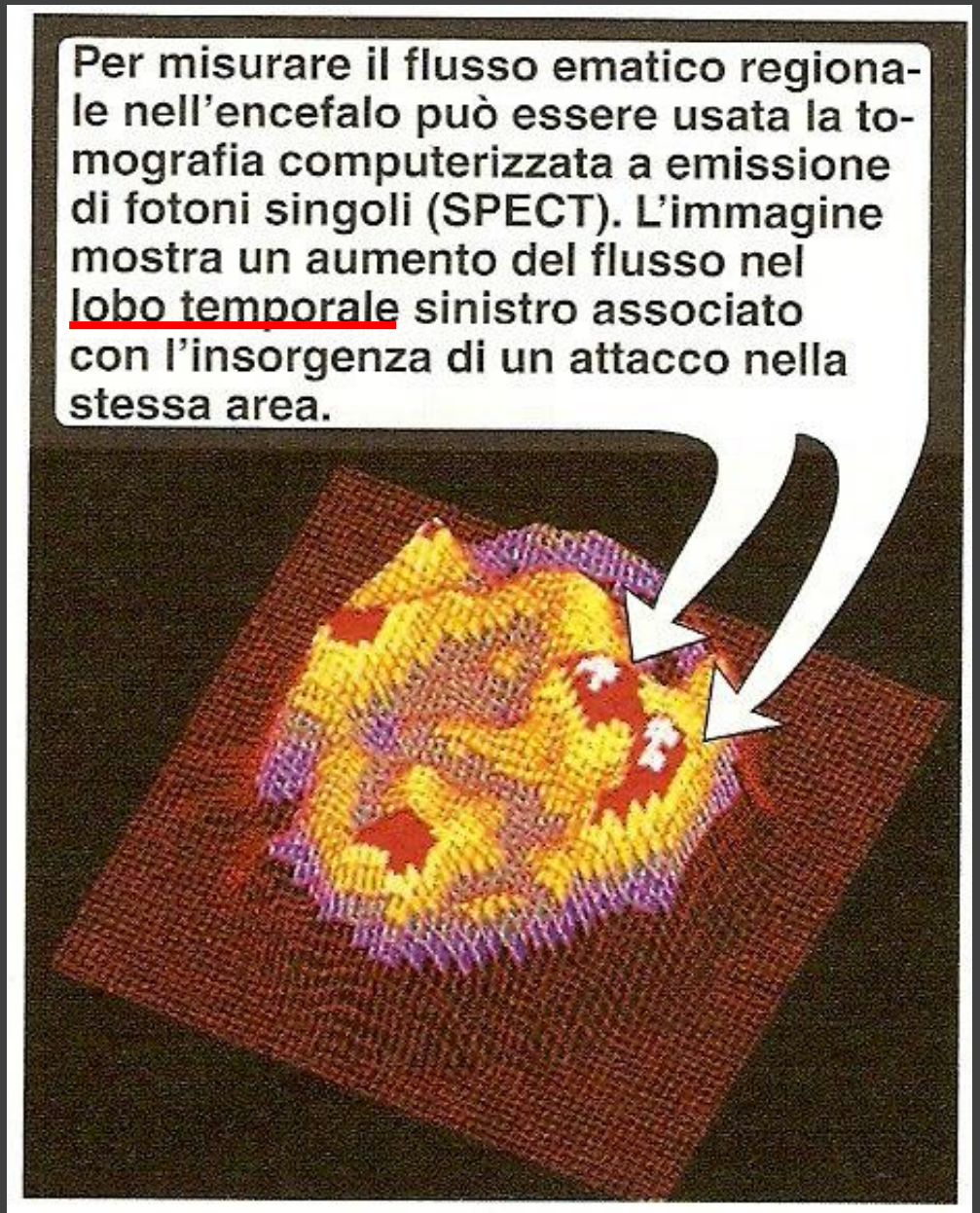
"After I have a seizure, I get an overwhelming sense that everything I know intellectually
to be in the present is distant in time and space,
like the sort of sense associated with the recollection of an old memory.
I have a powerful sense of anguish, pain, and loneliness."

Diagnosis

EEG in epilepsy



Regional blood flow during epilepsy seizure



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 (50/100.000pazienti)

Epilepsy genes

- 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 $\alpha 4$ 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 (Na^+, K^+).

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

Pharmacology

History

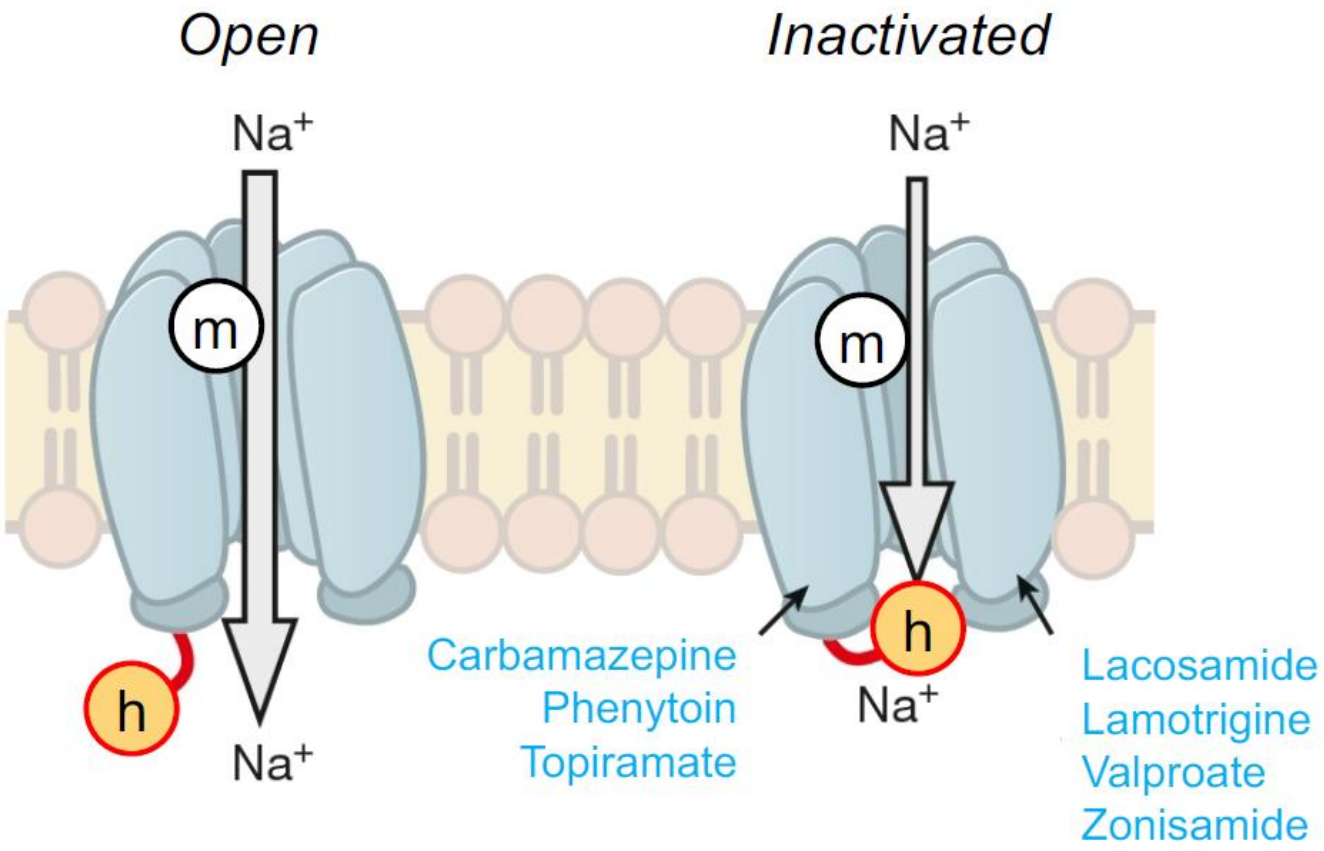
ante-1857	Folklore (epilepsy: taking possession; sacre disease)
1857	Bromide (K)
1912	Fenobarbital
1938	Fenitoine
1951	Ethosuximide
60 /70th	Carbamazepine, Benzodiazepine, Valproate
90th	New antiepileptics:
	Vigabatrine, Lamotrigine, Gabapentine, Felbamate, Oxcarbazepine

SEIZURE TYPE	FEATURES	CONVENTIONAL ANTISEIZURE DRUGS	RECENTLY DEVELOPED ANTISEIZURE DRUGS
PARTIAL SEIZURES:			
Simple partial	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. **Key feature is preservation of consciousness.**	Carbamazepine, phenytoin, valproate	Gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, zonisamide
Complex partial	Impaired consciousness lasting 30 seconds to two minutes, often associated with purposeless movements such as lip smacking or hand wringing.	Carbamazepine, phenytoin, valproate	Gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, zonisamide
Partial with secondarily generalized tonic-clonic seizure	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.	Carbamazepine, phenobarbital, phenytoin, primidone, valproate	Gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, zonisamide

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

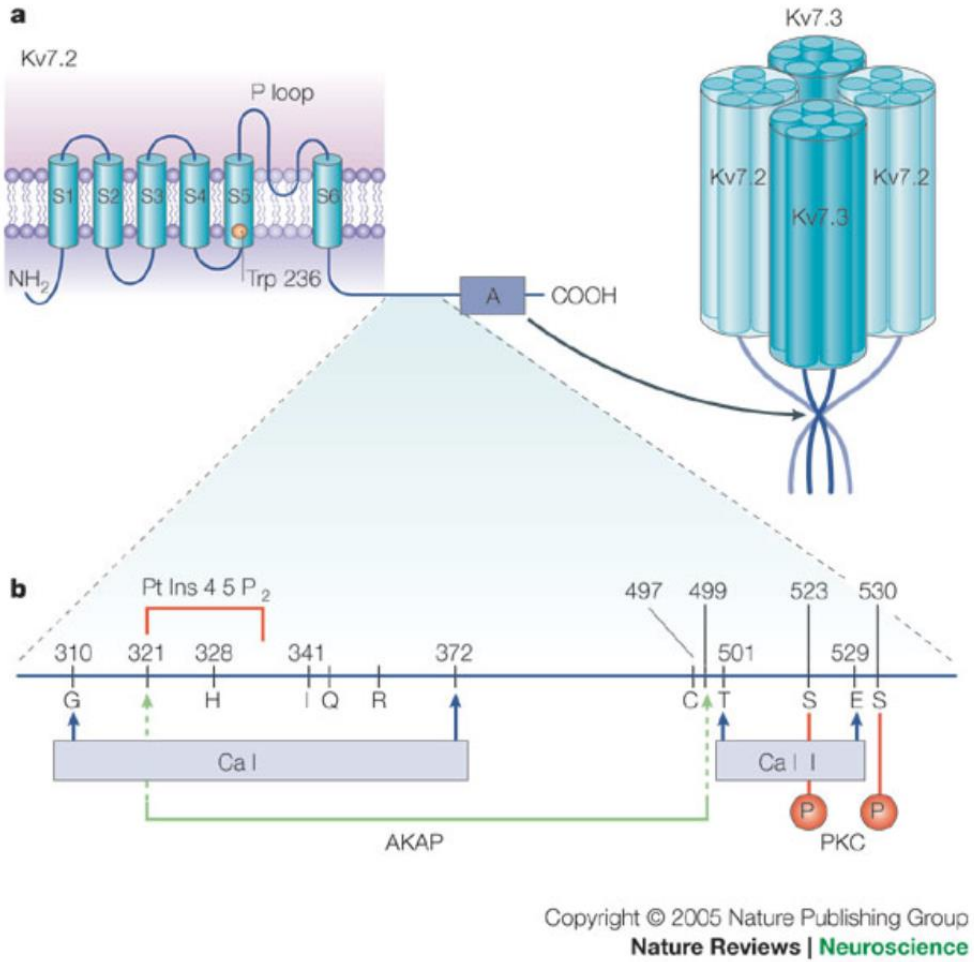
First target: sodium channels



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.



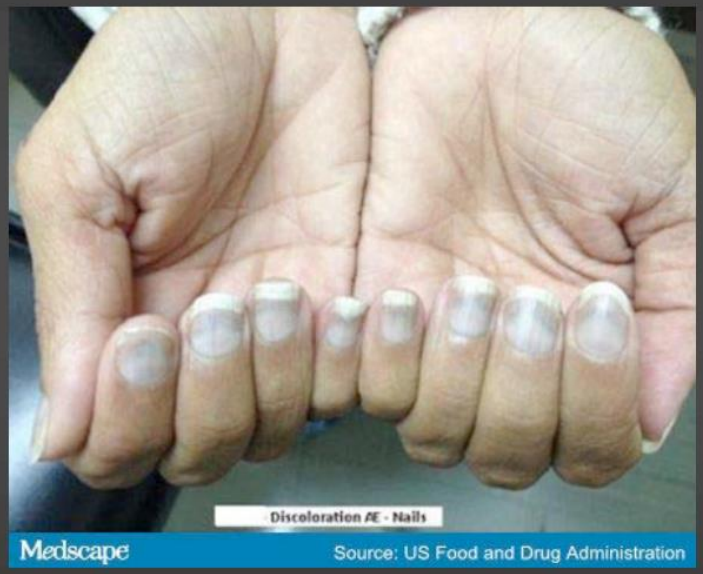
RETIGABINE: a *potassium channel opener* (neuronal potassium channel Kv7).

focal and tonic-clonic generalized seizures

RETIGABINE

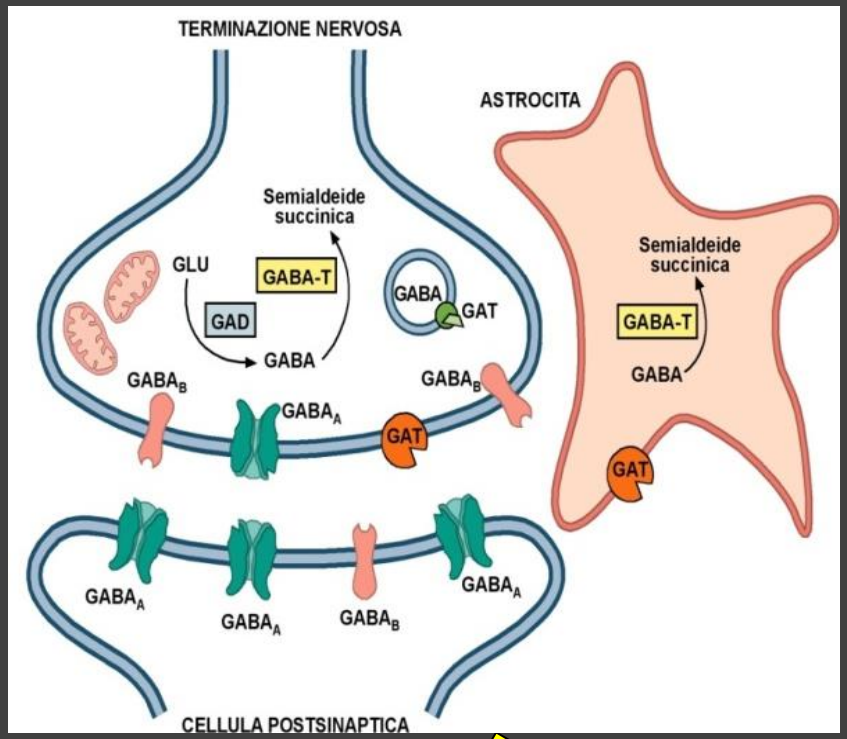
Side effects

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

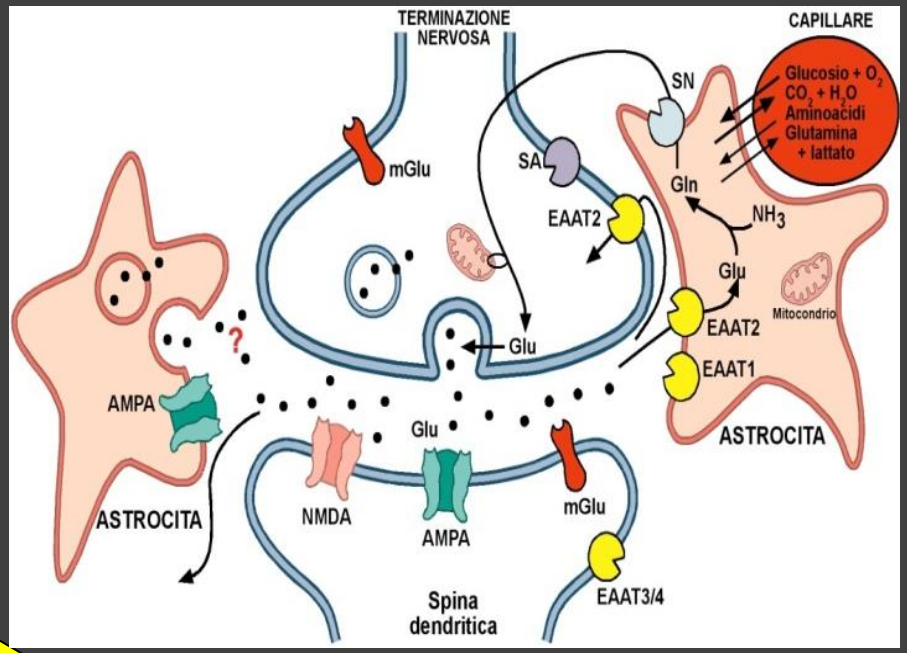


- Prolonged QT interval ➔ attention to cardiopathic patients and ECG monitoring

Molecular basis of Epilepsy



GABA



Glutamate

Third target: GABA

GABAergic system

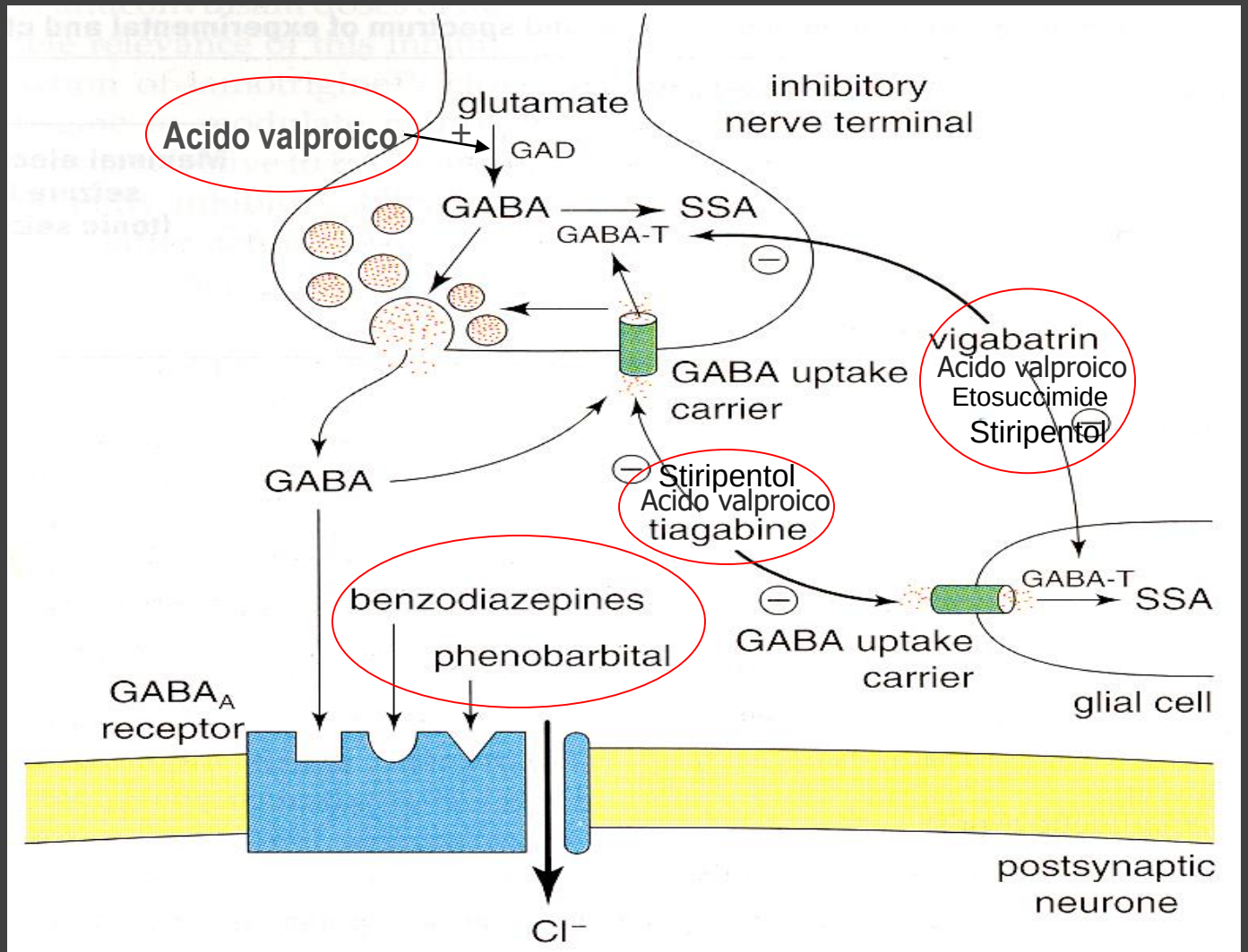
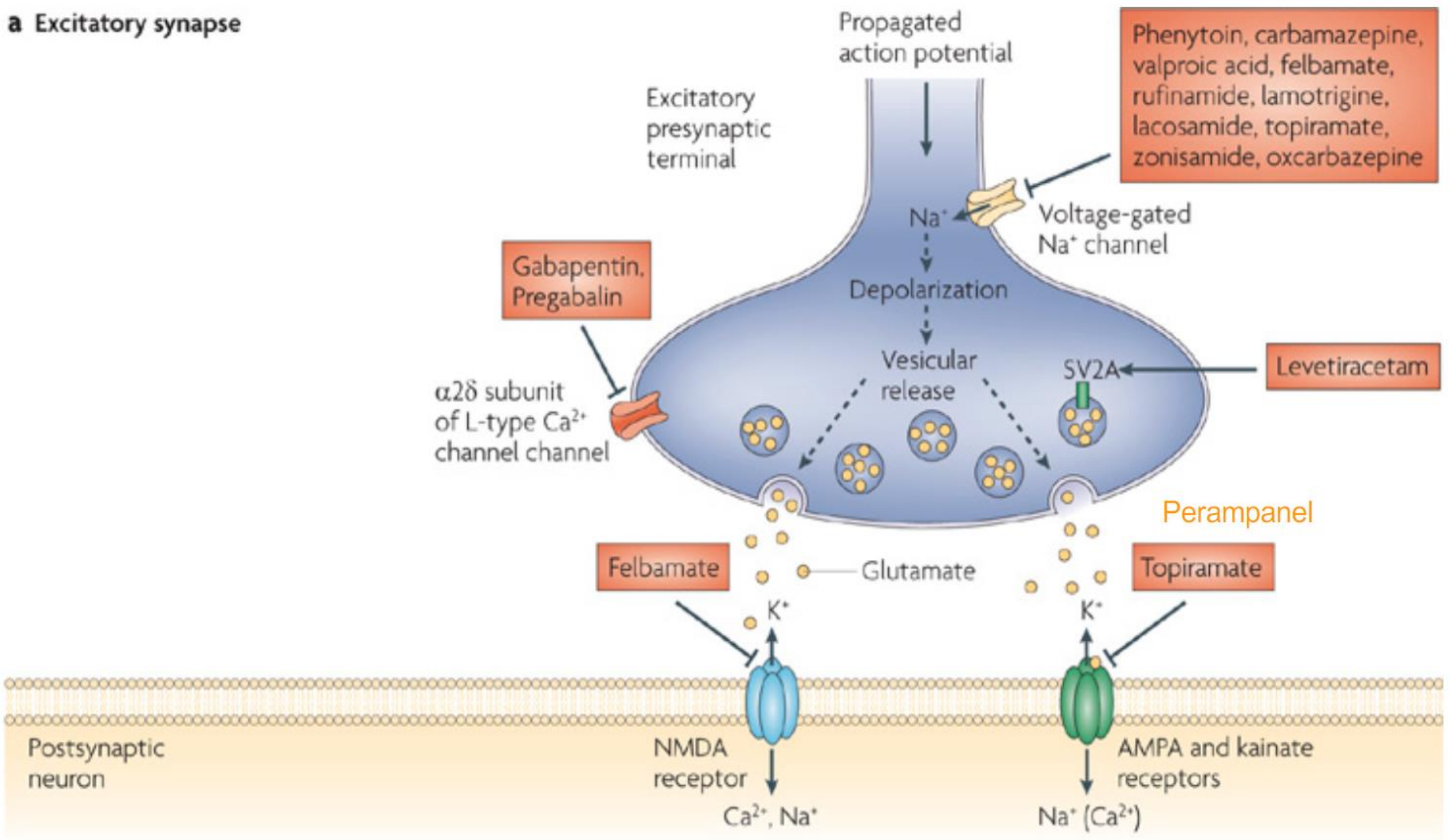


Fig. 2. Possible sites of interaction of antiepileptic drugs on GABA-mediated transmission. GABA is formed from glutamate by the action of glutamic acid decarboxylase (GAD), and can be metabolized by GABA aminotransferase (GABA-T) to form succinic acid semialdehyde (SSA). The $GABA_A$ receptor is associated 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 $GABA_A$ 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.**

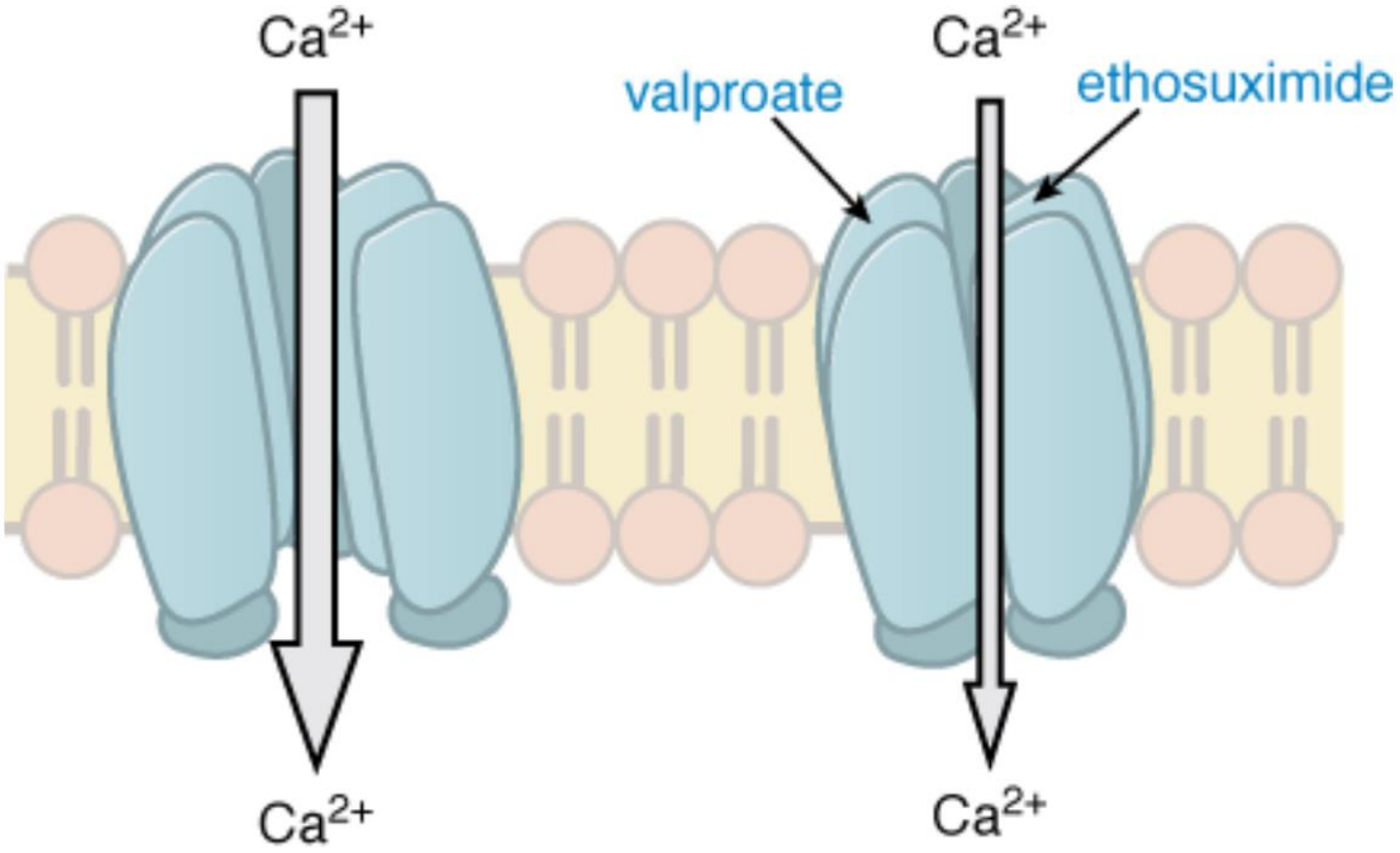
Fourth target: glutamatergic synapses



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



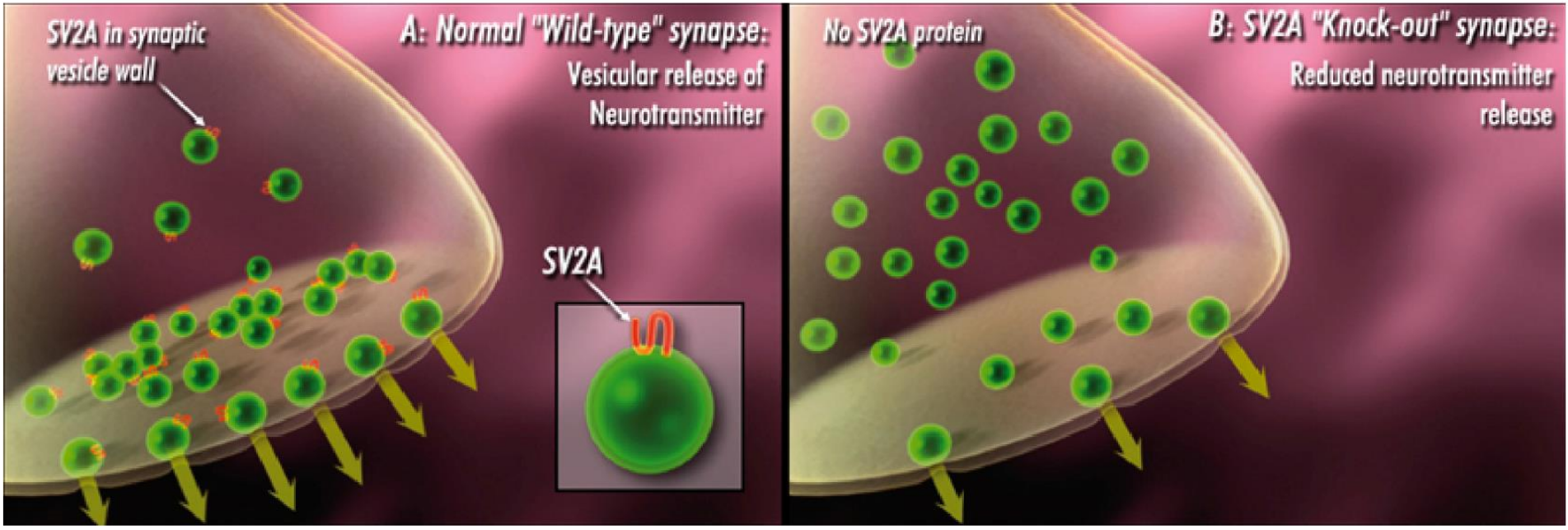
Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

AED that are active on absence seizures (ETHOSUXIMIDE, VALPROATE) reduce T-type Ca^{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 + 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.

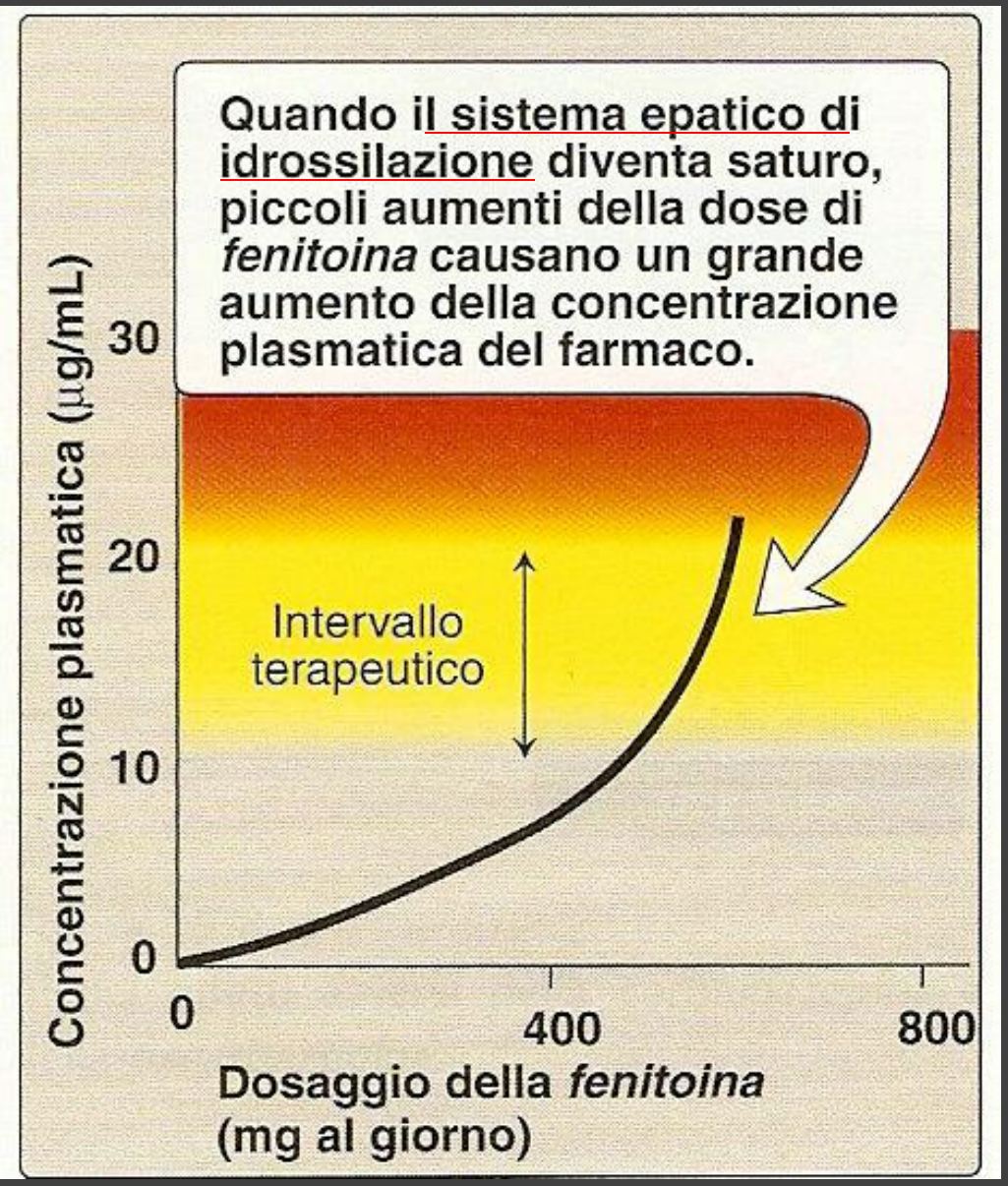
- **Carbamazepine**:
  - —derivative of tricyclic antidepressants
  - —similar profile of that of phenytoin, but with fewer unwanted effects
  - —effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor epilepsy; also useful in trigenimal neuralgia
  - —strong 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 *Phenythoin* on plasma concentration



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

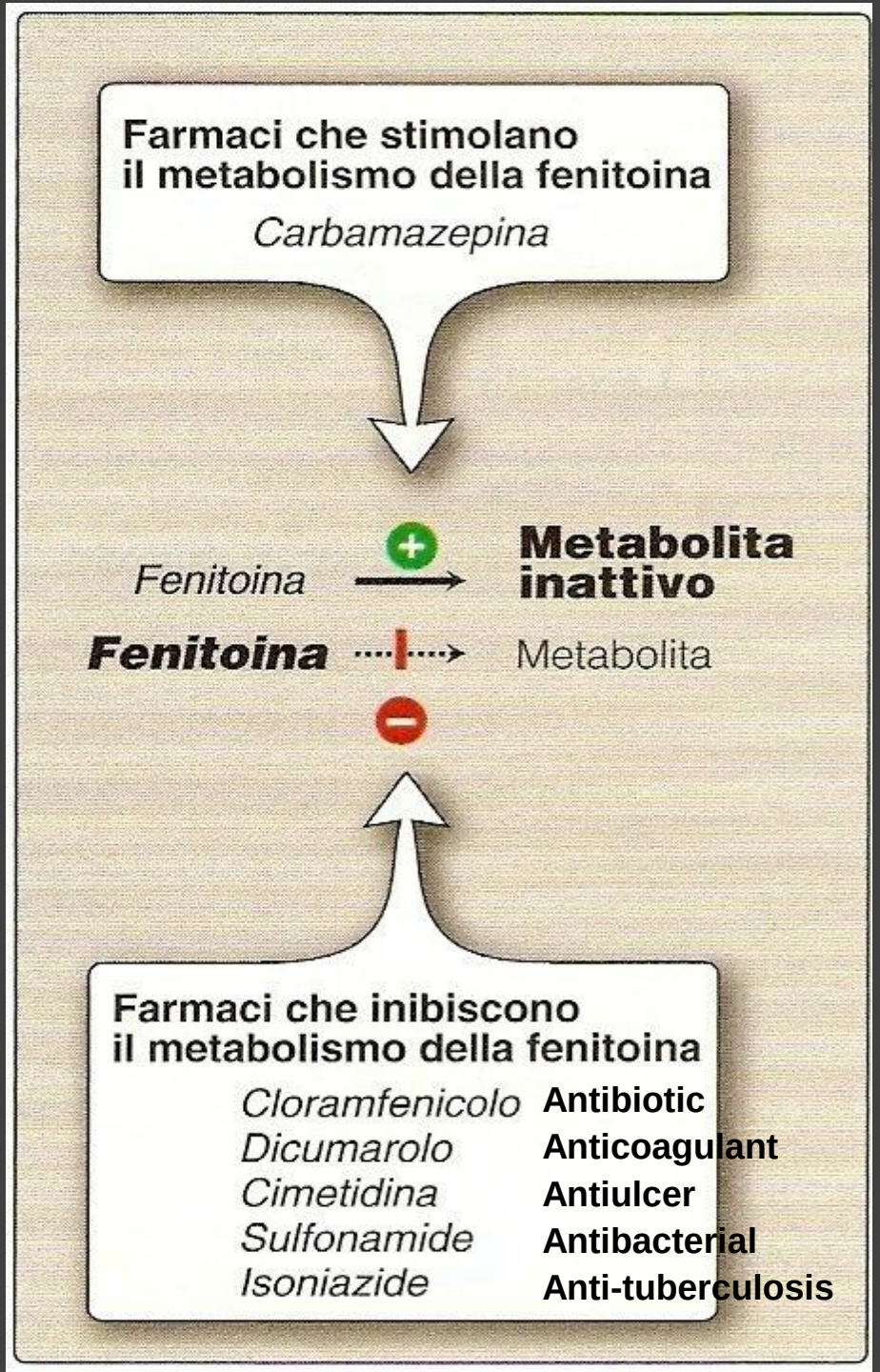
Inactive metabolites
<5% escretion unchanged
T ½ 24 hours

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



Phenytoine

induces P-450

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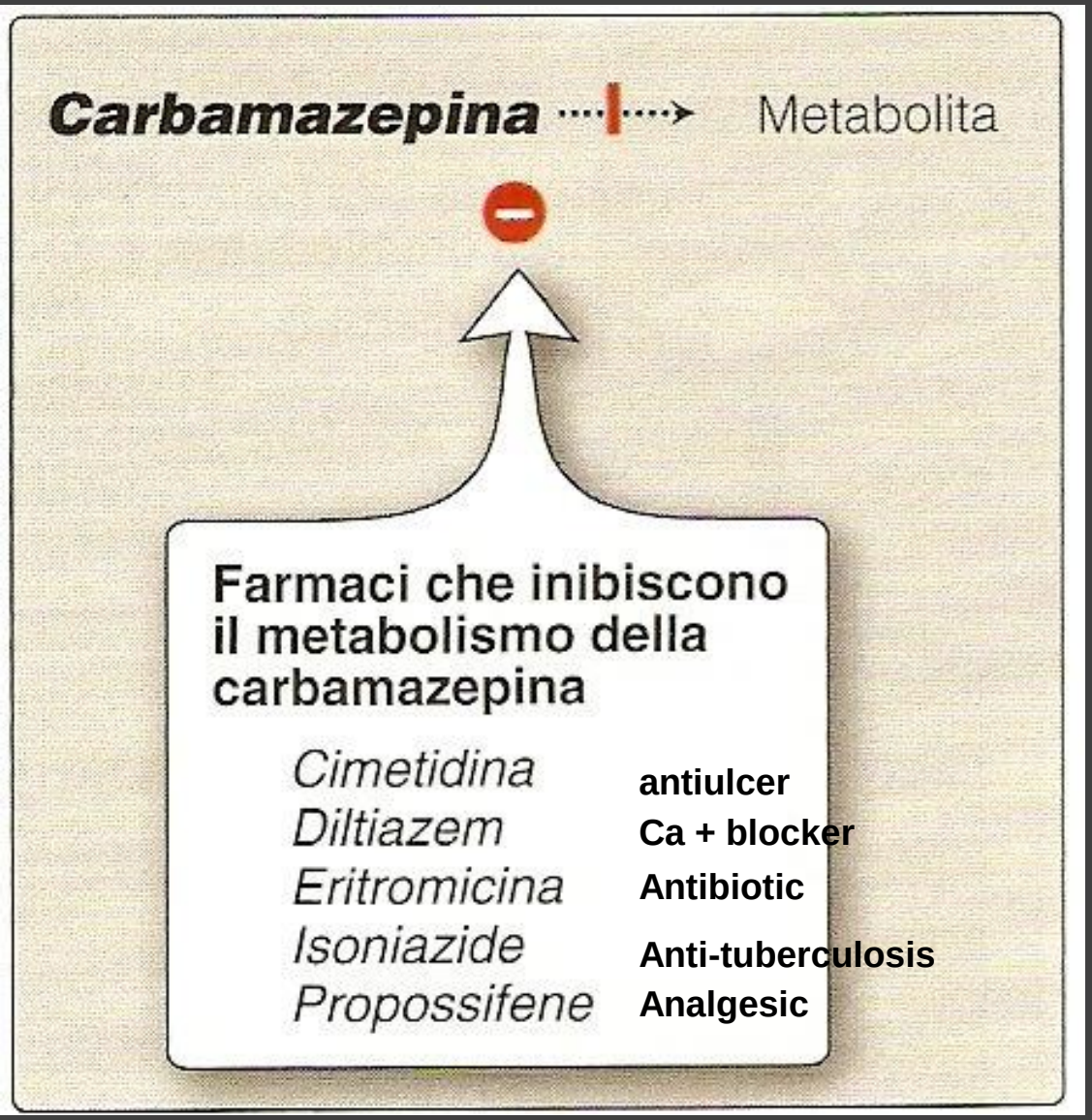
CARBAMAZEPINE



↑ CYP3A4

↓ Decrease concentration of:

carbamazepine

oral contraceptives

benzodiazepines

antidepressants

antibiotics

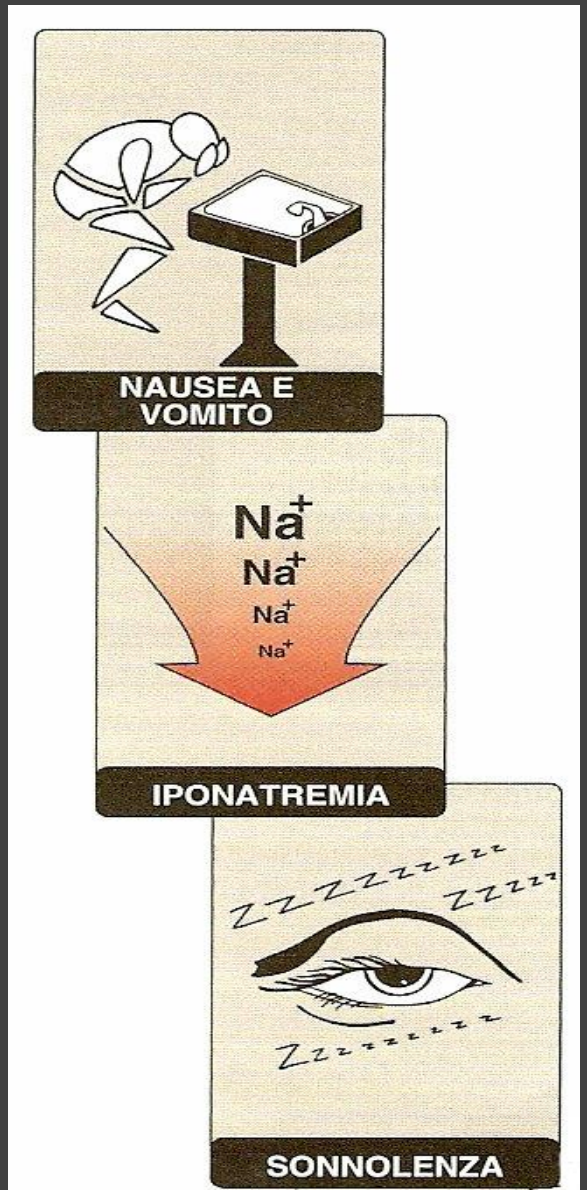
phenytoin

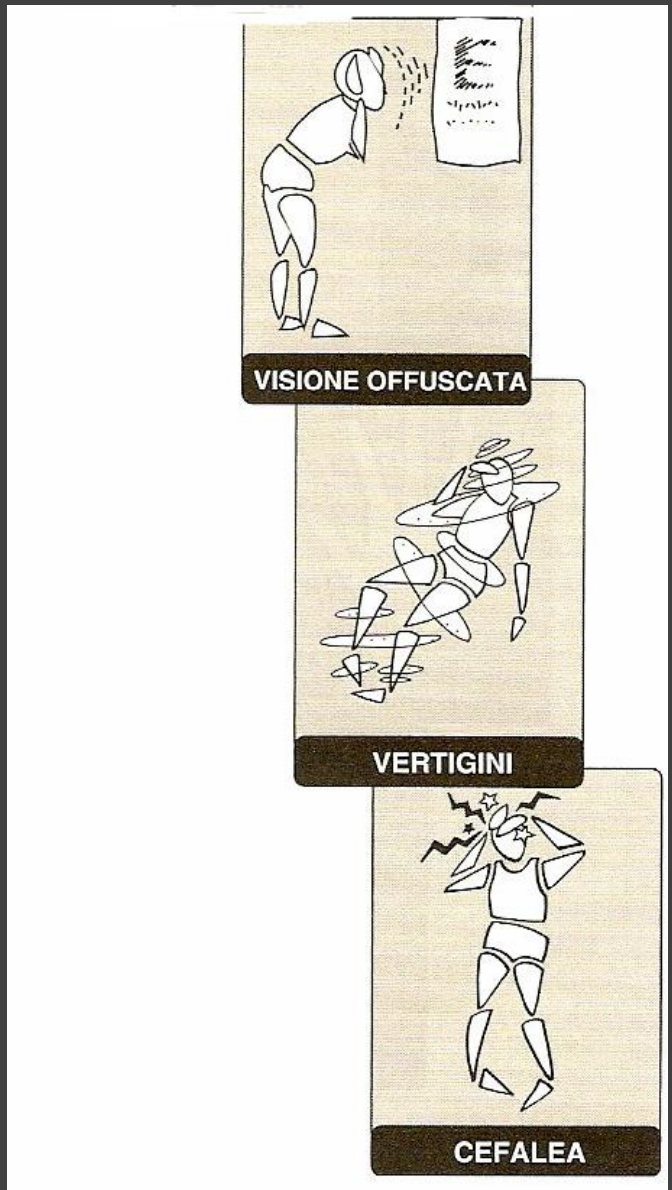
corticosteroids

warfarin

Metabolite 10,11-epoxide: blood dyscrasias (leukopenia, aplastic anemia), liver toxicity

Side effects of *carbamazepine* and *oxcarbazepine*





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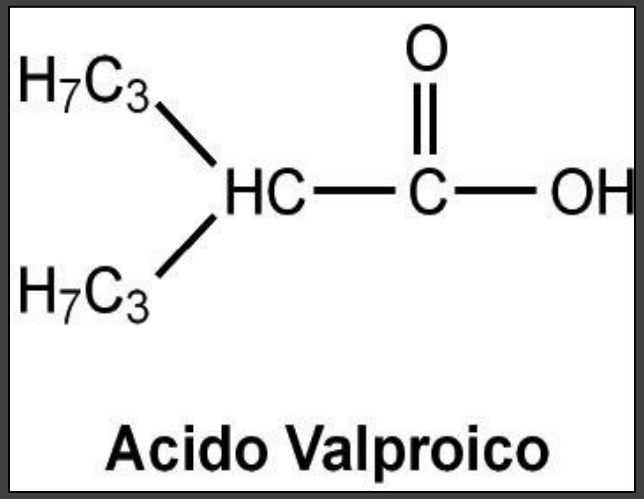
VALPROIC ACID (VP)



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:

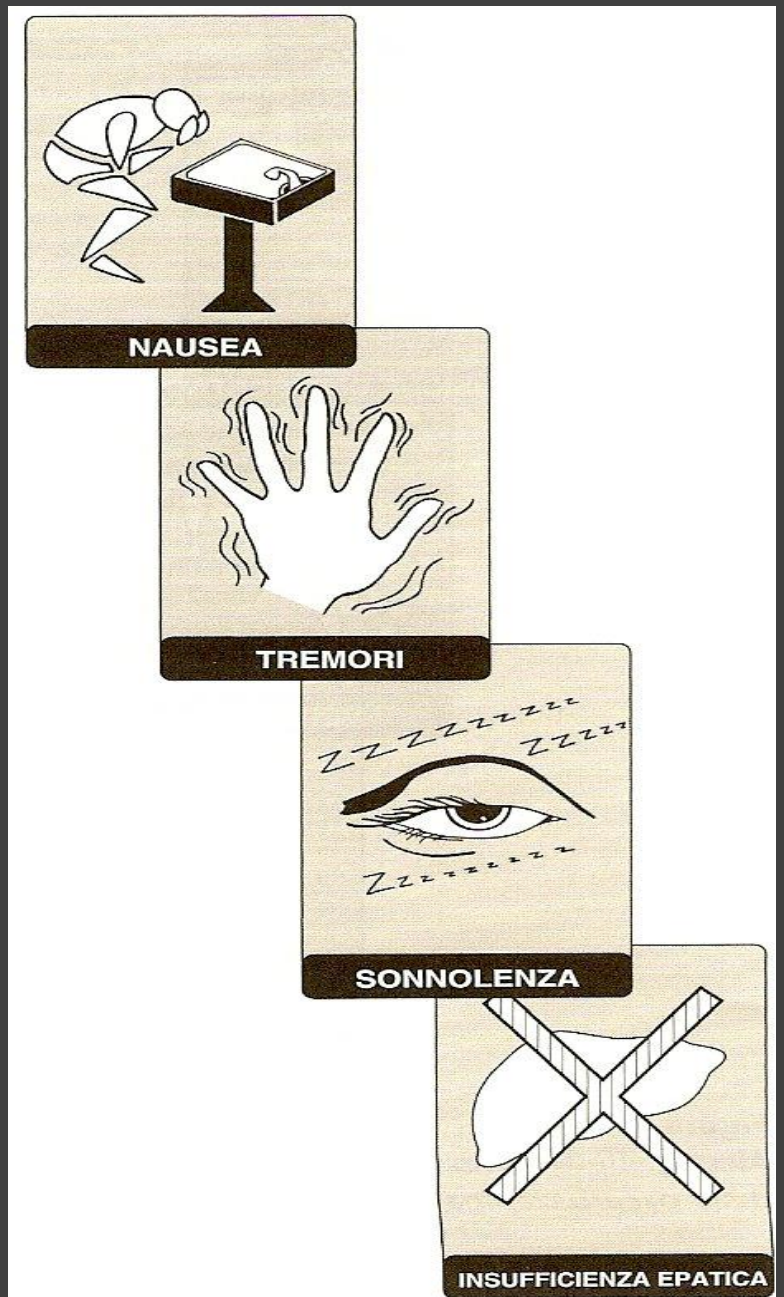
- **Rapid absorption**
- **90% plasma protein binding**
- **Metabolized liver (active metabolites), does not induce P-450**
- **Escretion urine glucuronidate. Unchanged 3%**

Side Effects

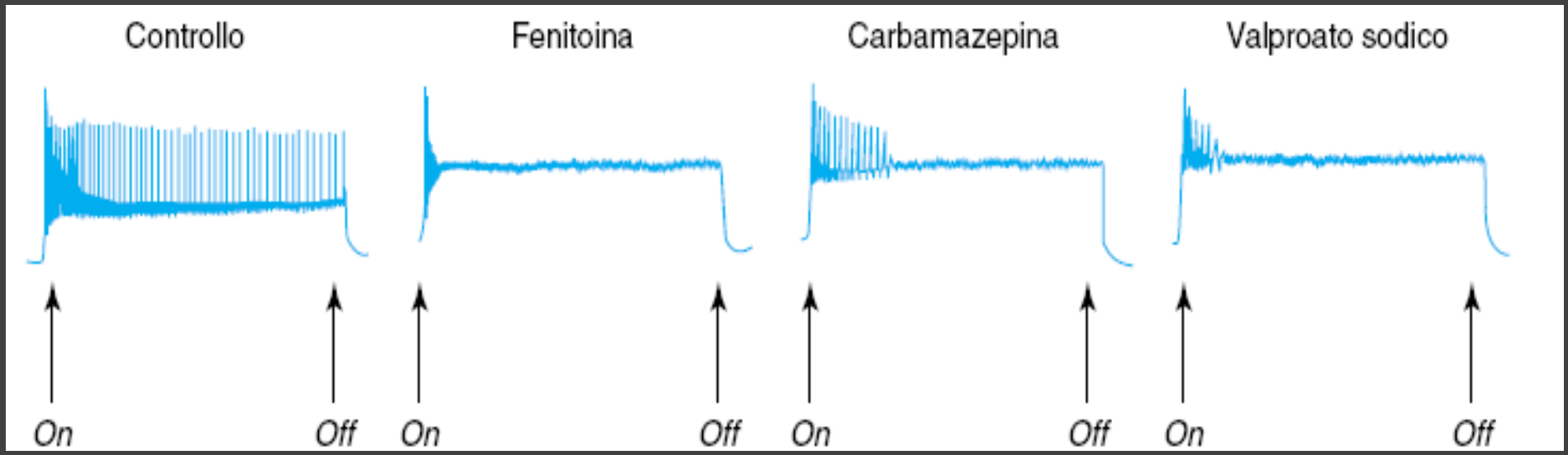
- Thrombocytopenia, platelet aggregation inhibition (bleeding), teratogenesis, liver damage

Inhibits phenobarbital metabolism, carbamazepine, etosuccimide

Side effects of *valproic acid*



EFFECT OF SOME ANTIEPILEPTIC DRUGS ON REPETITIVE NEURONAL DISCHARGE



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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

LAMOTRIGINE

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)

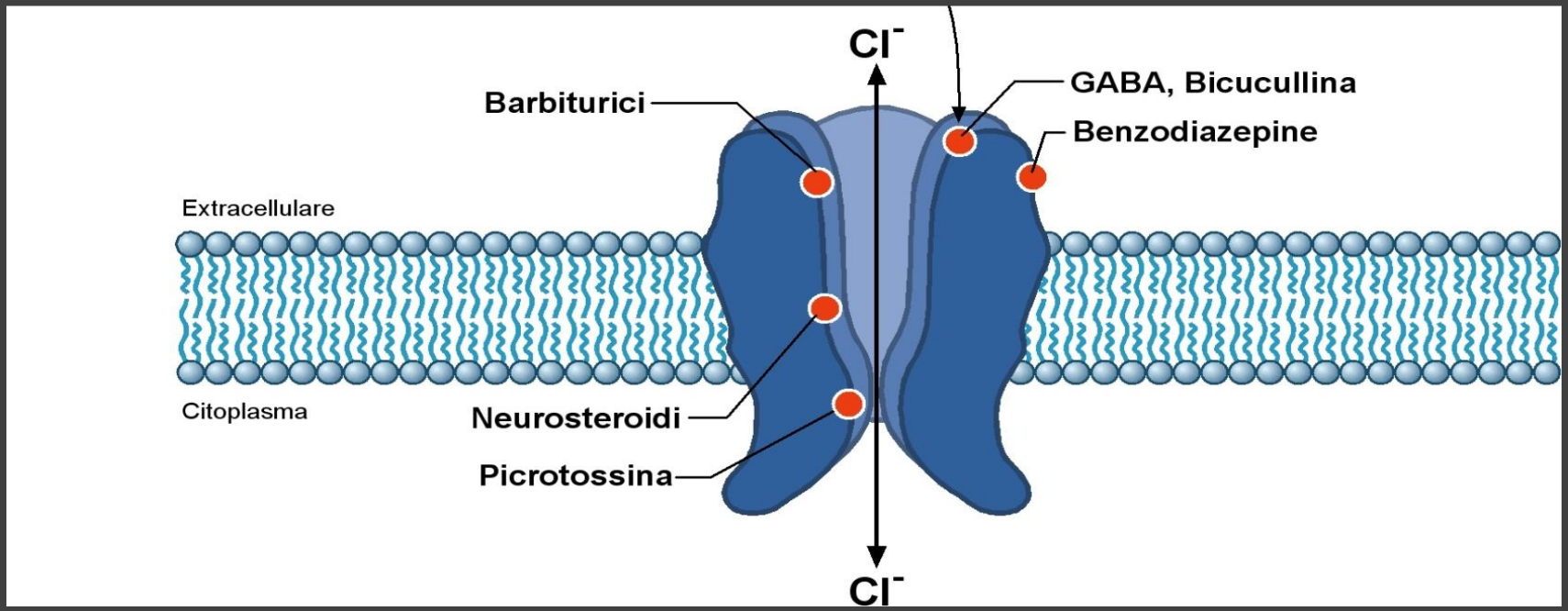
Side effects

- 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



Phenobarbital and primidone

Farmacokinetic:

Complete not rapid absorption

75% metabolized in liver (inactive metabolites), induces P-450

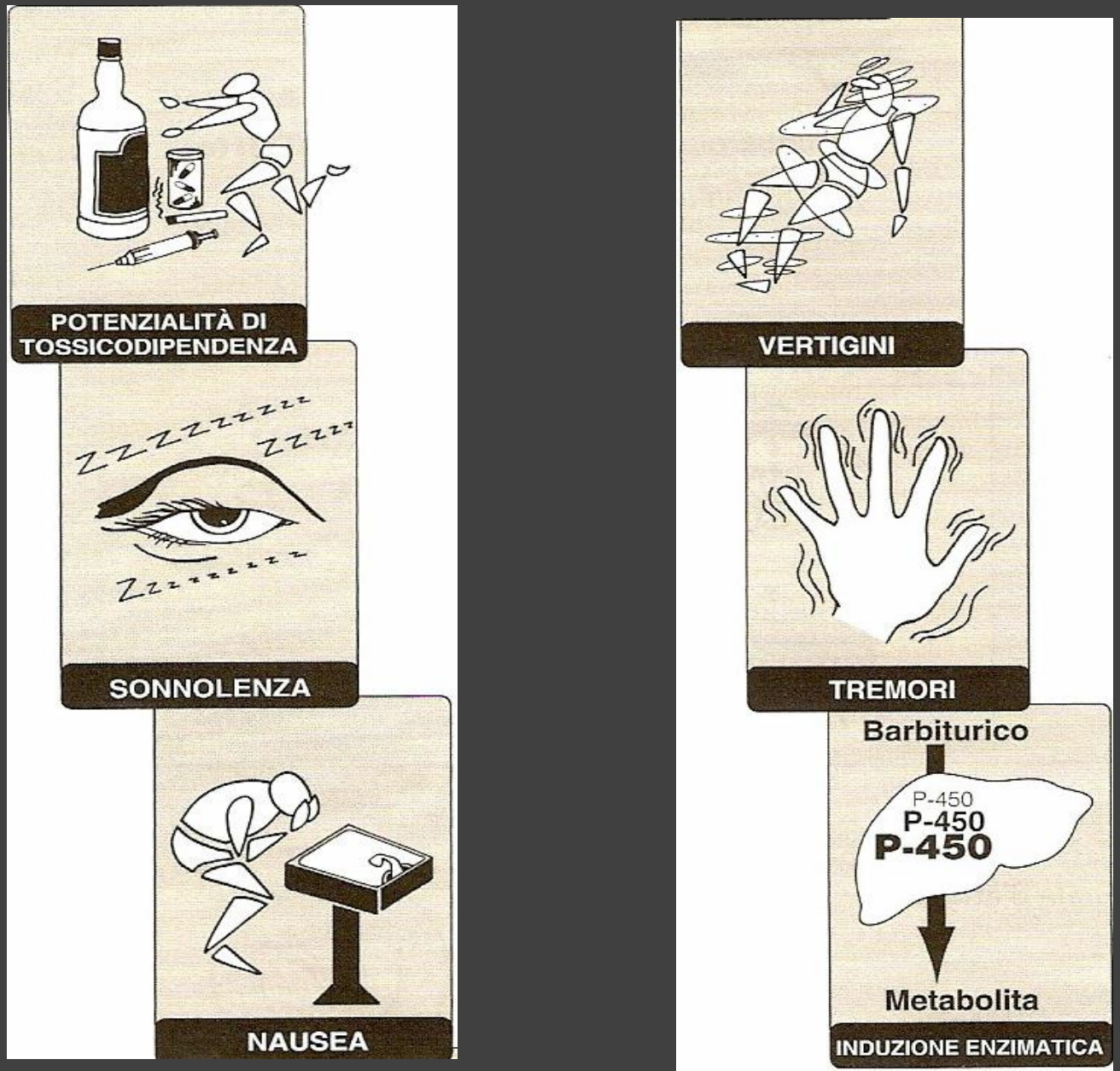
Primidone: partially transformed into phenobarbital

Side effects

Sedation, ataxia, vertigo. With high doses, agitation and confusion

After suspending convulsive rebound attack

Side effects of barbiturates



MAIN MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

Farmaco	Meccanismo d'azione			
	Blocco dei Canali del Na^+	Blocco dei Canali del Ca^{2+}	Attivazione della Neurotrasmissione GABAergica	Altri Meccanismi
Fenitoina	+++			
Carbamazepina	+++			
Oxcarbazepina	+++			
Fenobarbital	+	+	+++	+
Etosuccimide		+++	+ blocco GABA-T	+ blocco Na^+/K^+ ATPasi
Acido valproico	+	+	+	+ attivazione canali del K^+
Benzodiazepine			+++	
Gabapentina		++ LVA, $\alpha_2\delta$		
Lamotrigina	+++	+		
Topiramato	++	+	+	+ antagonismo recettori AMPA
Tiagabina			+++ inibizione GAT-1	
Zonisamide	+	++		
Felbamato	++		++	++ antagonismo recettori NMDA
Levetiracetam		+	+	+++ Legame al SV2A
Vigabatrin			+++ inibizione GABA-T	

Caratteristiche farmacocinetiche

Farmaco	Legame proteine (%)	Emivita (ore)	Posologia (mg/kg/die)	Intervallo terapeutico (µg/ml)	Indicazioni	Tossicità
Fenitoina	90	24 (dose-dipendente)	3-5	10-20	Epilessie parziali; tonico-cloniche generalizzate; no nelle assenze	Segni cerebellari (atassia, vertigini, nistagmo); reazioni ematologiche; iperplasia gengivale; irsutismo; osteomalacia; deficit di vit K
Carbamazepina	70	8-26	10-20	6-12	Epilessie parziali semplici e complesse; tonico-cloniche generalizzate; no nelle assenze	Segni cerebellari (atassia, diplopia); reazioni ematologiche (anemia aplastica, agranulocitosi); iponatremia
Oxcarbazepina	40% (derivato monoidrossilato MHD)	1-5 (oxcarbazepina) 7-20 (MHD)	8-13	15-35 (MHD)	Monoterapia o add-on dell'epilessie parziali dell'adulto e come add-on delle analoghe forme del bambino.	Iponatremia (più comune negli anziani); rash cutaneo
Fenobarbital	40-60	25-140	1.5-3.5	15-40	Tutti i tipi di epilessie; no nelle assenze	Sedazione; possibili interazioni per attività di farmacoinduzione; tolleranza e dipendenza fisica
Etosuccimide	0	30-40	15-25	40-80	Assenze; no nelle epilessie tonico-cloniche	Sintomi gastrointestinali (nausea, vomito, diarrea); SNC (letargia, cefalea, segni extrapiramidali); reaz. immunologiche ed ematologiche
Acido valproico	94	8-15	20-40	40-100	Epilessie parziali e generalizzate; antimioclonico	Sintomi gastrointestinali (nausea, vomito); SNC (atassia, tremore); tossicità epatica; teratogenesi
Benzodiazepine	98 diazepam 85 clonazepam	1-2 diazepam; 20-48 clonazepam 14 lorazepam	0,1-0,2 clonazepam	20-70	Tutti i tipi di epilessie; mioclonie; stato epilettico	Sedazione; incoordinazione motoria e atassia; tolleranza e sindrome da astinenza
Gabapentina	0	6-9	10-25	25-50	Epilessie parziali dell'adulto	Peggioramento crisi miocloniche; sonnolenza; modificazioni del comportamento (aggressività); obesità
Lamotrigina	55	24-35	4-8	1.5-10 (concentrazione bersaglio iniziale	Epilessie parziali e generalizzate (spesso in add-on)	Vertigini; sedazione; rash cutaneo; vomito (alte dosi); peggioramento epilessia mioclonica dell'infanzia (SMEI)

Main pharmacokinetic properties, indications and toxicity of antiepileptic drugs

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

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

Farmaco	Induzione Farmacometabolica	Inibizione farmacometabolica
Fenitoina	CYP2C e 3A;UGT	CYP
Carbamazepina	CYP1A2, 2C9, 2C19, e 3A4; UGT	—
Oxcarbazepina	CYP3A4	CYP2C19, UGT (debole)
Fenobarbitale	CYP1A2, 2C9, 2C19, e 3A4;UGT	—
Etosuccimide	—	—
Acido valproico	—	CYP2C9, 2C19;UGT 1A4
Benzodiazepine	—	—
Gabapentina	—	—
Lamotrigina	UGT	—
Topiramato	CYP3A4 (debole)	CYP2C19
Tiagabina	—	—
Zonisamide	—	—
Felbamato	CYP3A4 (debole)	CYP2C19
Levetiracetam	—	—
Vigabatrin	—	—

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 e neural tube defects.
2. High plasmatic concentrations, or poli-therapy, increase the risk of malformation.
3. More recent drugs are not teratogenic in animals.