Drugs affecting the central nervous system

15. Antiepileptic drugs (AEDs)

Epilepsy is caused by the disturbance of the functions of the CNS. Although epileptic seizures have different symptoms, all of them involve the enhanced electric charge of a certain group of central neurons which is spontaneously discharged during the seizure. The instability of the cell membrane potential is responsible for this spontaneous discharge. This instability may result from:

- increased concentration of stimulating neurotransmitters as compared to inhibiting neurotransmitters
- decreased membrane potential caused by the disturbance of the level of electrolytes in cells and/or
- the disturbance of the function of the Na^+/K^+ pump when energy is insufficient.

Mutations in sodium and potassium channels are most common, because they give rise to hyperexcitability and burst firing.

Mutations in the sodium channel subunits gene have been associated with
- in SCN2A1; benign familial neonatal epilepsy
- in SCN1A; severe myoclonic epilepsy of infancy
- in SCN1A and SCN1B; generalized epilepsy with febrile seizures

The potassium channel genes KCNQ2 and KCNQ3 are implicated in some cases of benign familial neonatal epilepsy.

Mutations of chloride channels CLCN2 gene have been found to be altered in several cases of classical idiopathic generalized epilepsy suptypes: child-epilepsy and epilepsy with grand mal on awakening.

Mutations of calcium channel subunits have been identified in juvenile absence epilepsy (mutation in CACNB4; the B4 subunit of the L-type calcium channel) and idiopathic generalized epilepsy (CACN1A1).

Mutations of $GABA_A$ receptor subunits also have been detected.

The gene encoding the $\alpha 1$ subunit, GABRG1, has been linked to juvenile myoclonic epilepsy; mutated GABRG2, encoding an abnormal γ subunit, has been associated with generalized epilepsy with febrile seizures and childhood absence epilepsy.

15.1. The mechanism of action of antiepileptic drugs

Generally, the following manners of epilepsy therapy are possible:

- the stabilization of the membrane potential of nervous cells by the modification of the properties of the ion channels responsible for the rest and action potential
- the restoration of the physiologic equilibrium between the stimulating and inhibiting neurotransmitters, for example by enhancing the GABA concentration or lowering the glutamate concentration.

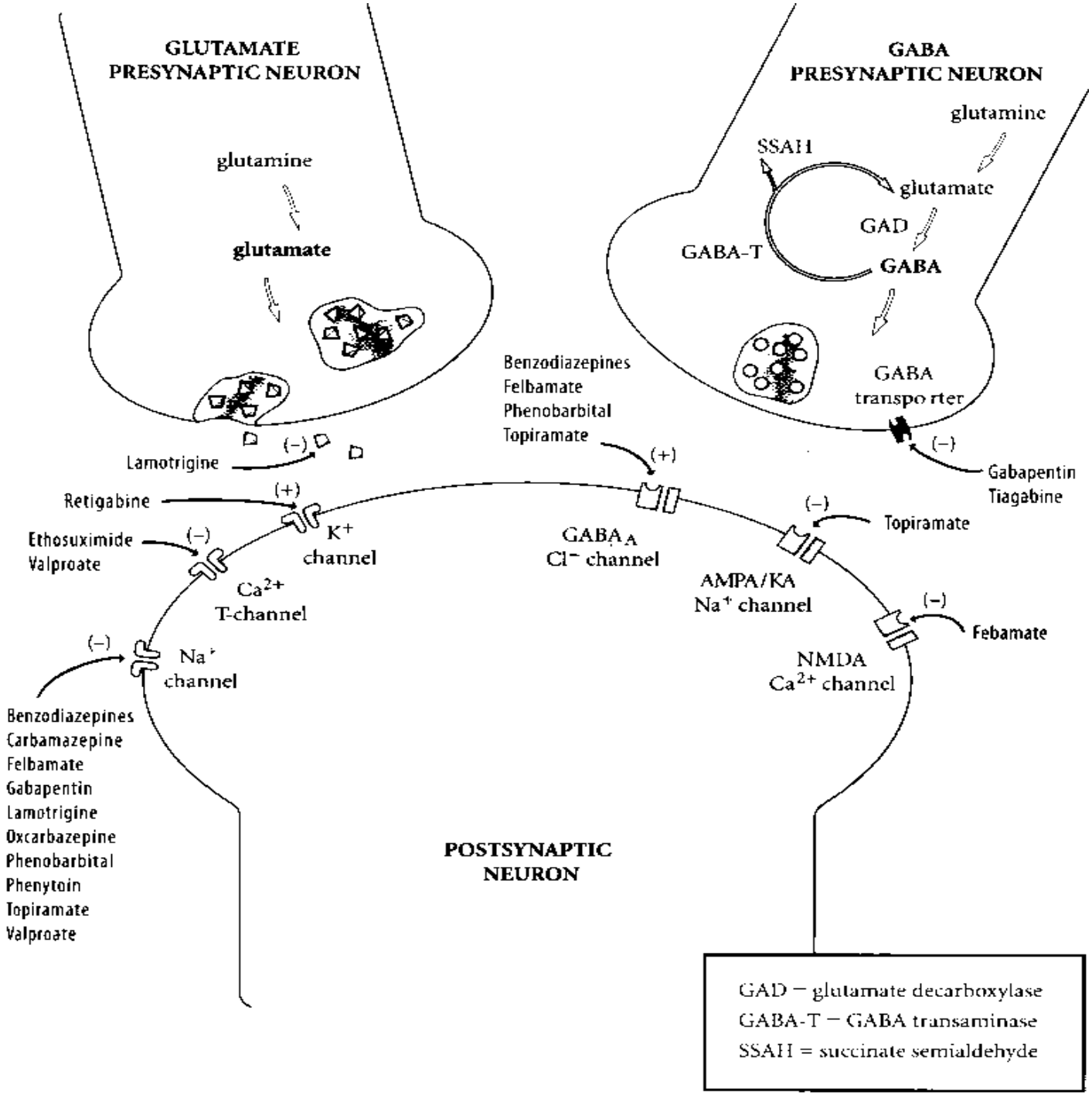
15.2. The classification of (AEDs)

Criterion – mechanism of action (1)

1. Potential dependent ionic channels modulators
   - sodium channel inhibitors: hydantoine derivatives (phenytoin, phosphenytoin, ethotoin, mephenytoin), iminostilbenes (carbamazepine, oxcarbazepine), other derivative: topiramate, valproate, lamotrygine, zonisamide, felbamate,
   - potassium channel modulator: retigabine
   - calcium channel inhibitors: etosuximide and valproate (T-type), gabapentin and pregabalin (L-type)
2. Modulators of ligand dependent ionic channels
   - $GABA_A$ Cl^- channel: benzodiazepines (diazepam, clonazepam, lorazepam, clorazepate dipotassium, midazolam), barbituric and deoxybarbituric acid derivatives (phenobarbital, mephobarbital, primidone), felbamate
   - NMDA Ca^{2+} channel: felbamate
   - AMPA/KA Ca^{2+} channel: topiramate

The classification of (AEDs)
Criterion – mechanism of action (2)

3. GABA transporter inhibitors: gabapentin, tiagabine
4. GABA-aminotransferase inhibitors: vigabatrin
5. AEDs which mechanism of action is not totally known: levetiracetam, sultiame


GLUTAMATE
PRESYNAPTIC NEURON
glutamine
glutamate
GABA
PRESYNAPTIC NEURON
glutamine
SSAH
glutamate
GAD
GABA-T
GABA
GABA
transpo rter
Benzodiazepines
Felbamate
Phenobarbital
Topiramate
(+)
(−)
Gabapentin
Tiagabine
Lamotrigine
(−)
Retigabine
(+)
K+
channel
Ethosuximide
Valproate
(−)
Ca2+
T-channel
GABAA
Cl− channel
(−)
Topiramate
AMPA/KA
Na+ channel
(−)
Febamate
NMDA
Ca2+ channel
(−)
Na+
channel
Benzodiazepines
Carbamazepine
Felbamate
Gabapentin
Lamotrigine
Oxcarbazepine
Phenobarbital
Phenytoin
Topiramate
Valproate
POSTSYNAPTIC
NEURON
GAD = glutamate decarboxylase
GABA-T = GABA transaminase
SSAH = succinate semialdehyde

The classification of (AEDs)

Criterion – chemical structure

In therapy of epilepsy the following are used:

- **hydantoine derivatives (Phenytoin, Fosphenytoin)**
- **dibenzazepine (iminostilben) derivatives (Carbamazepine, Oxcarbazepine)**
- **benzodiazepine derivatives (Clonazepam, Diazepam, Lorazepam, Clorazepate dipotassium)**
- **barbituric and hexahydropyrimidinedione derivatives (Phenobarbital, Mephobarbital, Primidone)**
- **bis-carbamates (Felbamate)**
- **imides (Phensuximide)**
- **sulfonamides (Zonisamide)**
- **GABA analogues (Vigabatrine, Gabapentin)**
- **other antiepileptics (Lamotrigine, Tiagabine, Retigabine, Topiramate, Valproic acid salts).**

The classification of (AEDs)

Criterion – Clinical application

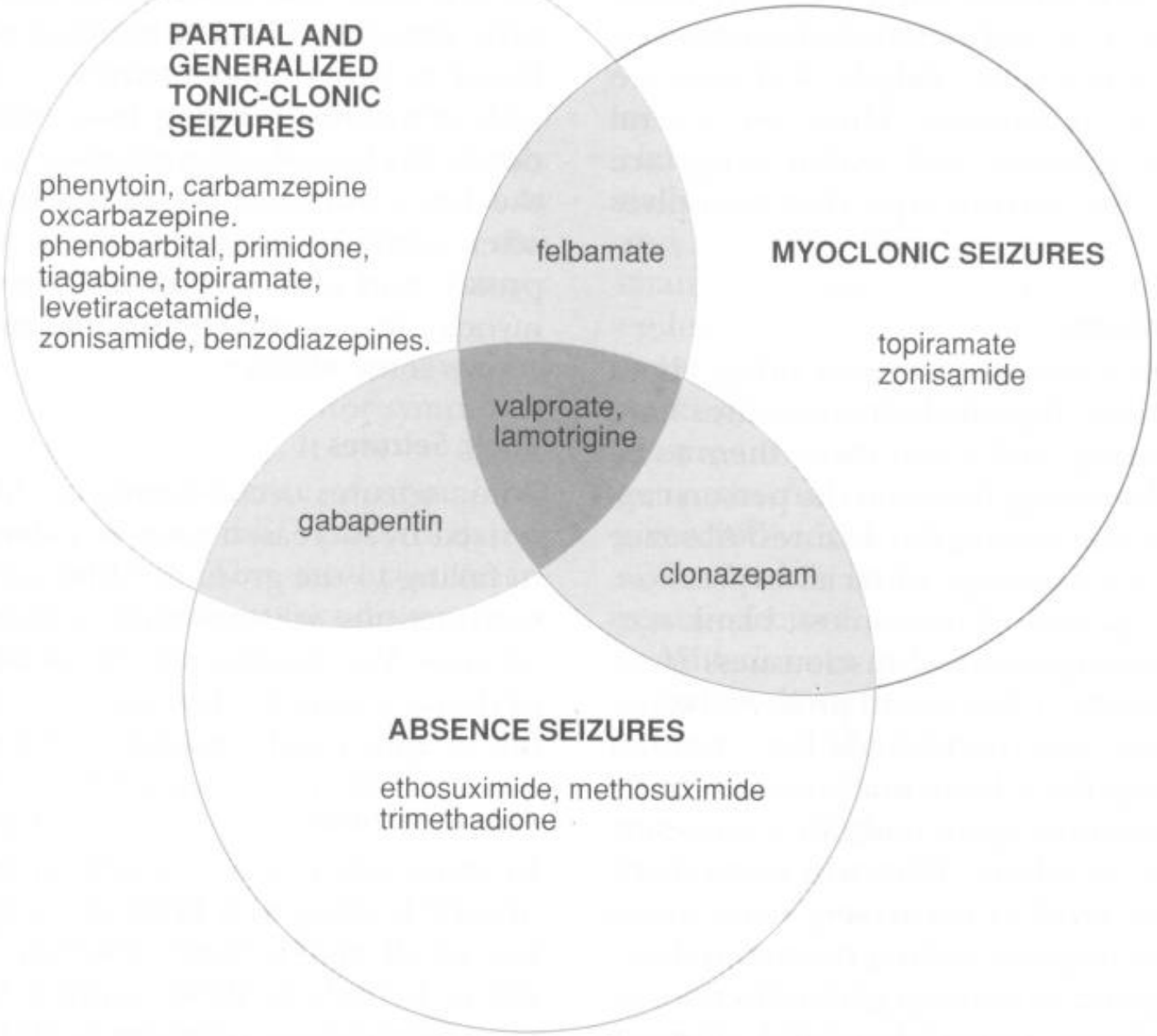
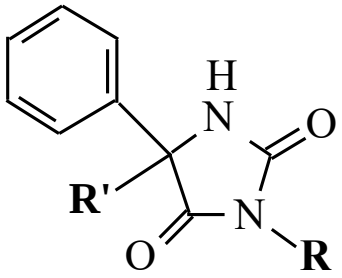


Fig. 20.1. The antiseizure drugs used in treatment of the various seizures.

15.2. Potential dependent ion channels inhibitors



Phenytoin, R = H, R' = C_6H_5

5,5-Diphenylimidazolidine-2,4-dion

Mephenytoin, R = -CH_3, R' = -C_2H_5

Fosphenytoin sodium; R = -$CH_2OPO_3Na_2$, R' = C_6H_5

Phenytoin can be considered as an imidazolidinedione or hydantoine derivative. Phenytoin has been introduced into therapy of epilepsy in 1938.
Phenytoin is indicated for initial adjunctive treatment of complex partial (psychomotor) or generalized tonic-clonic seizures and status epilepticus.
It is often selected for initial monotherapy due to its high efficacy and relatively low incidence of side effects.
Phenytoin is not used in the treatment of absence seizures as it may increase their frequency of occurrence. In contrast to the barbiturates it demonstrates only weak sedative action.

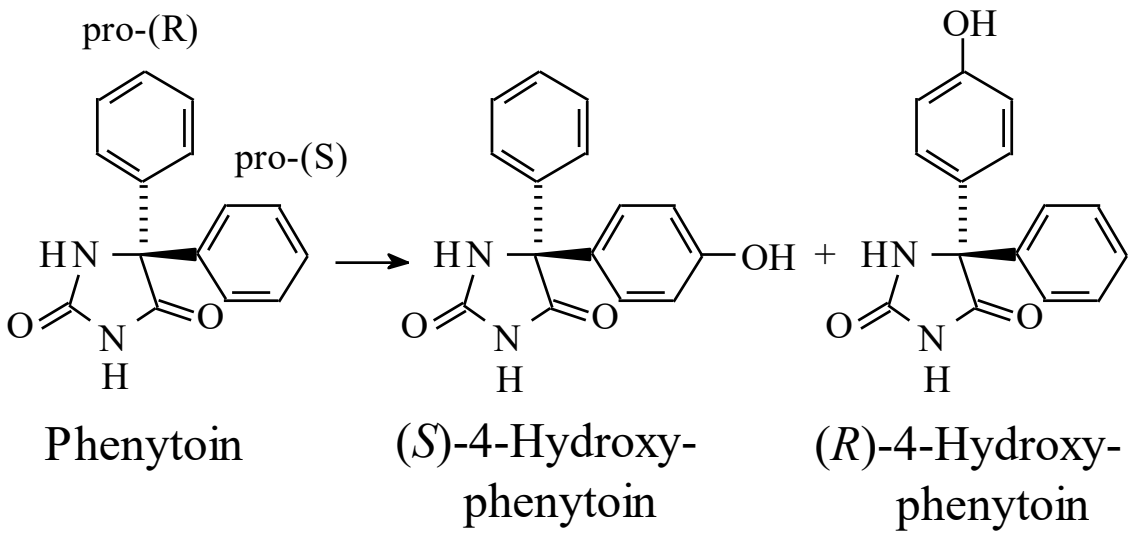
Phenytoin influences nervous function by decreasing membrane permeability for ions and the change of ATPase activity, synaptic transmission, the release of neurotransmitters and the metabolism of cyclic nucleotides.

For the treatment of epilepsy the blockade of the sodium channels by phenytoin is crucially important.

When phenytoin is administered orally, it is absorbed slowly and not completely.
The bioavailability of phenytoin, ranging from 20-90%, depends on the technological process and particle size.
Its maximal concentration in plasma is reached after 3–12 h. Approximately 90% of the dose binds with plasma proteins, mainly albumins.

Phenytoin displaces other antiepileptic drugs, e.g. valproic acid, from their binding with proteins.

The main metabolite of phenytoin is 4-hydroxyphenytoin.



At doses below 10 μg/ml ($t_{0.5}$ = 6–24 h) elimination occurs as a first-order reaction. At higher concentrations elimination dependent on the dose is observed and half-time of elimination elongates to 60 h.

As a result of that a non-linear relationship between the dose and its concentration in plasma is observed.

In practice it is possible to obtain a good correlation between the concentration of phenytoin in plasma and its therapeutic effect.

Because patients differ considerably in their metabolism of phenytoin, it is necessary to determine the concentration of phenytoin in each patient's plasma to find an optimal dose. It is very important because of the low therapeutic index of phenytoin (2.0).

The *N*-methyl derivative of phenytoin (*Mefenytoin*) acts similarly to phenytoin, but it is more toxic.

Fosphenytoin is a pro-drug which is soluble in water and stable in this environment.
It is used IM and IV. Indications for its use are similar to those of phenytoin.
In the body fosphenytoin is metabolised to phenytoin as result of dephosphorylation and oxidative demethylation with the release of a formaldehyde molecule.

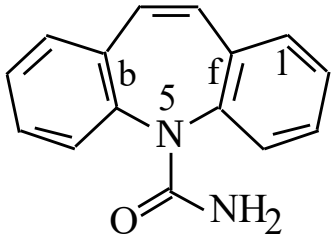
The main adverse effects of phenytoin and its derivatives:

- central nervous system effects are most frequent and include nystagmus, ataxia, dysarthria and sedation
- gingival hyperplasia, usually reversible
- hirsutism (in 10% of patients)
- idiosyncratic reactions such as rash, agranulocytosis, thrombocytopenia, lymphadenopathy, Stevens-Johnson syndrome and hepatitis
- too rapid IV administration of phenytoin sodium can result in severe hypotension and fatal cardiotoxicity.

The incidence of phenytoin toxicity may be increased in the elderly and in those patients with hepatic or renal impairment because of alterations in its pharmacokinetics.
Additionally, phenytoin demonstrates immunosupressive activity.

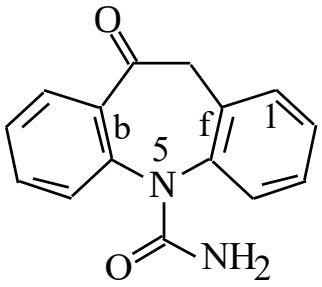
Phenytoin is also used as an anti-arrhythmic drug (since 1950), mainly in arrhythmia caused by therapy with cardiac glycosides.

Dibenzazepine (iminostilbene) derivatives



Carbamazepine, AMIZEPIN, NEUROTOP, TEGRETOL

5-Carbamoil-5*H*-dibenz[b,f]azepine



Oxcarbazepine, TRILEPTAL

10,11-Dihydro-10-oxo-5*H*-dibenz[b,f]azepine-5-carboxamide

Carbamazepine, similarly to phenytoin, inactivates the sodium channel causing the stabilization of the cell membrane.

Additionally, it inhibits phosphorylation of proteins regulated by the Ca^{2+}-calmoduline system and, because of that, it influences the release of the inhibiting neurotransmitters.

Carbamazepine is indicated in initial or adjunctive therapy for complex partial, tonic-clonic and mixed-type seizures.
Alongside phenytoin it is one of the two safest and most effective drugs of the older AEDs for these seizure types and is chosen for monotherapy due to high effectiveness and relatively low incidence of side effects.

The adverse effects:

- common toxicities include blurred vision, dizziness, drowsiness, ataxia and headache
- tremor, depression and cardiac disturbances are seen at high serum concentration
- idiosyncratic rashes are common; rarer severe idiosyncratic effects include anemia, agranulocytosis, thrombocytopenia and jaundice
- gastric upset from carbamazepine may be diminished by taking the drug after meals.

Allergic reaction, somnolence, vertigo, nystagmus and sometimes the damage of bone marrow are less common than in the case of therapy with phenobarbital and phenytoin.

Carbamazepine after oral administration is absorbed slowly. Its maximal concentration in plasma is observed after 4–8 h, and at higher doses this time elongates to 24 h. Approx. 95% of the dose binds with plasma proteins.

A linear relationship between the dose and the concentration in plasma is not observed. Therapeutic index of carbamazepine is 2.0 and because of that patients receiving carbamazepine should have periodic blood count determinations and liver function tests. Blood levels should be monitored in patients with renal or hepatic impairment.

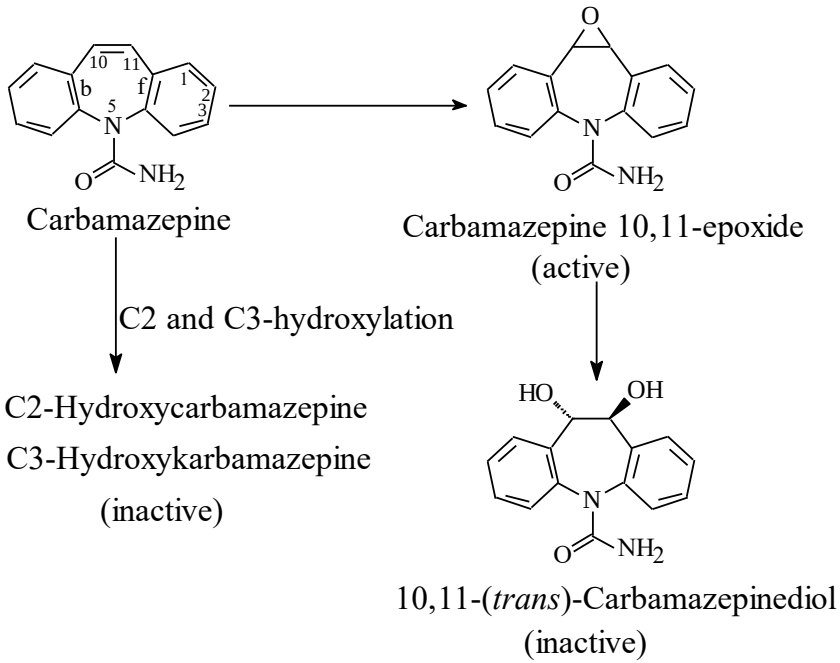
Carbamazepine increases phenytoin levels and decreases levels of felbamate, lamotrigine, valproate, zonisamide, theophylline and oral contraceptives.

Carbamazepine levels are increased by erythromycin, chloramphenicol, isoniazid, verapamil, propoxyphene and cimetidine.

Carbamazepine levels are decreased by phenobarbital, phenytoin, felbamate and primidone.

The metabolism of carbamazepine. Carbamazepine is principally metabolized by CYP3A4 to active carbamazepine 10,11-epoxide, which is more toxic than carbamazepine. Its concentration in plasma and in the brain is approx. 50% of that of carbamazepine.

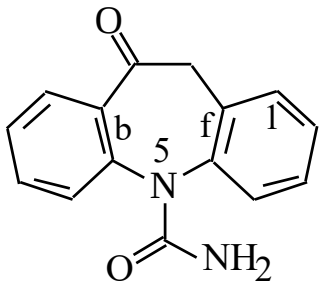
10,11-Epoxide is hydrolysed to inactive 10,11-dihydroxycarbamazepine by epoxide hydrolase. The hydroxylation products at positions C2 and C3 of the aromatic ring do not demonstrate antiepileptic activity. About 72% of an oral dose is excreted in the urine as metabolites and 3% as unchanged drug. The 28% found in the feces may be the result of incomplete absorption and enterohepatic cycling. In long-lasting therapy, the half-time of carbamazepine elimination is 10–20 h.

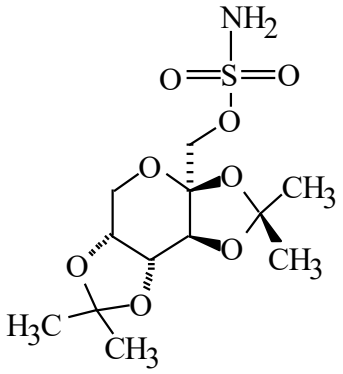


Oxcarbazepine is the 10-keto analog of carbamazepine and is indicated as monoterapy or adjunctive therapy for partial seizures in adults with epilepsy and adjunctive therapy for the treatment of partial seizures in children 4-16 years of age with epilepsy.

Its mechanism of action is similar to that of carbamazepine but less potent. It is metabolized to active 10-monohydroxycarbazepine and its glucuronide, inactive 10,11-dihydroxycarbazepine (4%).

In the case of oxycarbazepine it does not form carbazepine-10,11-epoxide.





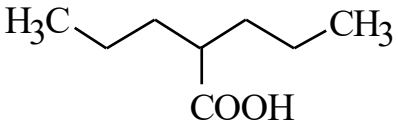
Topiramate, TOPOMAX

Topiramate (sulfamate-substituted monosaccharide, derived from fructose) demonstrates a broad spectrum of AED activity. It is approved for monotherapy or as an adjunct drug for partial or primary generalized tonic-clonic seizures in patients older than 10 years, as adjunct therapy in children aged from 2 to 10 years with partial-onset seizures, and in persons older than 2 years with Lennox-Gastaut syndrome. Topiramate also is approved for the prophylaxis of migraine headaches.

It blocks repetitive firing by acting on sodium channels, may enhance $GABA_A$–mediated chloride flux and, probably, it is an antagonist at the AMPA and kainate receptors, blocking in this way the effect of glutamate. Topiramate also blocks L-type calcium channels.

The bioavailability of topiramate after oral administration is 80–95%, the half-life is 20–30 h, approx. 70–80% of the dose is eliminated in the urine as unchanged drug.

The main adverse effects associated with topiramate therapy include CNS disturbance (drowsiness, dizziness, impaired concentration and memory, speech and language difficulties and confusion), weight loss and an increased incidence of renal stones.



Valproic acid, VALPROAL; 2-Propylpentanoic acid

Valproic acid is also used as sodium (APILEPSIN, DEPAKINE, VUPRAL) or magnesium (DIPROMAL) salt, and as amide (DEPOMIDE). Valproate is indicated for initial or adjunctive treatment for absence seizures or as an adjunct when absence seizures occur in combination with either tonic-clonic seizures, myoclonic seizures, or both.

Valproate block potential dependent sodium channels .
Valproic acid also increases the concentration of GABA in the brain by activation of glutamate decarboxylase and inhibition of GABA transaminase and succinic semialdehyde decarboxylase.

Valproic acid does not induce enzymes, so in contrast to phenytoin and phenobarbital it does not influence the metabolism of other drugs.

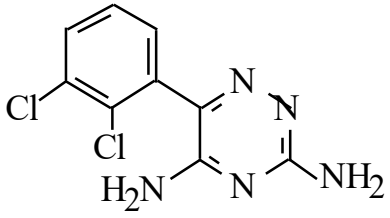
Valproate undergoes rapid and complete absorption. It reaches a maximal concentration in plasma after 1-4 h. Elongation of this time is observed when it is administered during meals and in the case of modified tablets. It is 90% protein-bound but its clearance is dose-dependent due to an increase in the free fraction of the drug at higher doses. It is eliminated in the urine as unchanged drug (less than 3%) and its acyl glucuronide conjugate (40% by mitochondrial β-oxidation and about 15-20% by ω-oxidation).

Valproate is metabolized almost entirely by the liver enzymes. The main metabolites are the result of glucuronidation of the carboxyl group, mitochondrial β- and ω-oxidation (to the main active metabolite, (E)-2-ene-valproate and 4-ene-valproate). The 4-pentene derivative is a reactive metabolite responsible for the hepatotoxicity of valproate. In the urine 3-oxo and 4-hydroxy valproate are also found.

The elimination half-time of valproate is 7–15 h and it may be reduced by other enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital) if they are administered together with valproate. Because of that during combined therapy AED plasma concentrations should be monitored. The theraputic concentration of valproate in plasma is 30–100 μg/ml.

Therapy with valproate may cause:

- CNS disturbances (confusion, anxiety, behavioral anomalies, depression, tremors, stupor)
- gastro-intestinal disturbances, which can be minimized by using enterically coated tablets
- reversible hair loss, weight gain
- coagulability disturbances (thrombocytopenia, inhibition of platelet aggregation and a lowered level of fibrinogen)
- liver function disturbances (rare but can have a fatal effect).



Lamotrigine, LAMICTAL

6-(2,3-Dichlorophenyl)-1,2,4-triazin-3,5-diamine

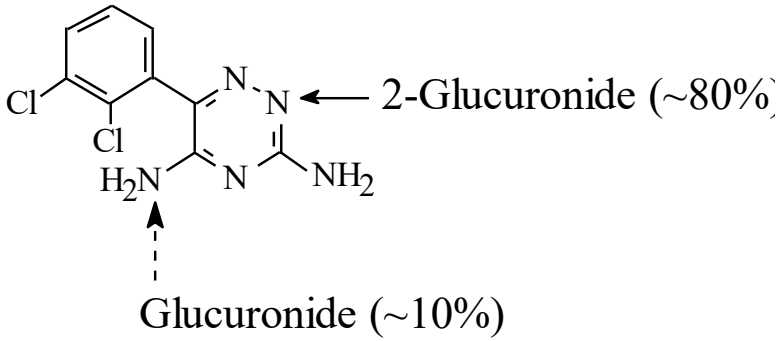
Lamotrigine is indicated in monotherapy or as an adjunct for partial seizures in adults and for adjunctive use in patients with Lennox-Gastaut syndrome. Additionally, it can be beneficial in combating myoclonic and typical absence seizures.

Lamotrigine inhibits an excessive release of glutamate by blocking voltage-dependent sodium channels. It does not influence potassium channels when normal release of glutamate is observed. It is thought that lamotrigine also affects calcium channels.

Lamotrigine administered orally is absorbed rapidly and completely (98%), exhibiting linear pharmacokinetics and modest protein binding (55%). Its maximal concentration in plasma is reached in 2-3 h.

Lamotrigine is metabolized predominantly to N-glucuronides (2-N-glucuronide (80-90%) and 5-amino-N-glucuronide (8-10%), which are eliminated in the urine.

8-10% of the dose is eliminated as unchanged drug.



The elimination half-time of lamotrigine is usually 24-35 h but it is reduced to 13-15 hours in patients taking enzyme-inducing AEDs (phenytoin, carbamazepin).

Valproate increases the half-life of lamotrigine by inhibiting N-glucuronidation.

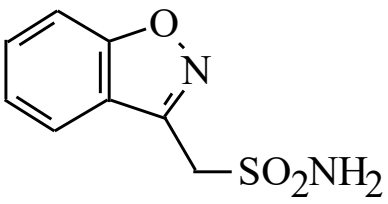
Because of that in the presence of valproate a dose of lamotrigine should be decreased to avoid toxicity.

Lamotrigine does not inhibit or induce liver metabolism.

The adverse effects associated with lamotrigine therapy include:

- serious rashes, which limit the usefulness of lamotrigine especially in children or patients taking valproate
- myoclonus after 2-3 years of treatment with this drug
- CNS disturbance – dizziness, diplopia, headache, ataxia, blurred vision, somnolence
- gastro-intestinal disturbance – nausea.

Sulfonamides



Zonisamide

Zonisamide is indicated as an adjunct for partial seizures in patients older than 16 years whose seizures are not controlled by first-line drugs.

Zonisamide (benzisoxazole derivative) blocks both sodium and T-type calcium voltage-dependent channels. Because it also affects dopaminergic transmission it may improve bipolar or schizoaffective disorder patients.

Zonisamide is also a carbonic anhydrase inhibitor.

Pharmacokinetics

The absorption for orally administered zonisamide is slow but nearly complete.

Pharmacokinetics is nonlinear.

The half-time:

- 50-70 hours, if is administered alone.
- 27 hours in the presence of phenytoin
- 38 hours in the presence of carbamazepine or phenobarbital
- 46 hours in the presence of valproate.

Metabolism

- more than one-third of oral dose is excreted in the urine in an unchanged form
- N-acetylation
- reduction by CYP3A4/CYP2D6
- metabolism to 2-sulfamoyloacetyl phenol

Metabolites are eliminated in the urine in an unchanged form or as glucuronides with an elimination half-life of 63 hours.

Adverse effects and contraindication

Zonisamide is contrindicated in patients with a history of allergy to sulfonamides (sulfonamides are associated with Stevens-Johnson syndrome).

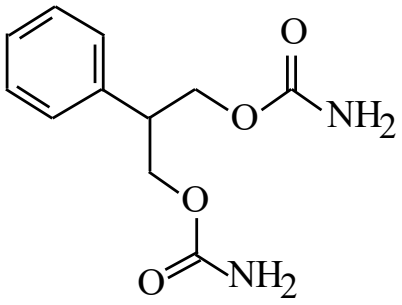
Zonisamide should be used with caution in patients with hepatic or renal disease.

It also has shown to be teratogenic in animal studies.

Adverse effects. Somnolence, anorexia, dizzines, agitation, confusion, headache, cognitive impairment, and memory loss.
In addition, an incidence of drug-induced psychosis has been noted.
The development of renal stones may occur with use of this drug.

Bis-Carbamates

Felbamate, TALOXA, FELBATOL



1. **Felbamate is used as a secondary-line drug when other AEDs are ineffective. It is reserved for severe refractory seizures, either partial, myoclonic or atonic, or in Lennox-Gastaut syndrome.**
2. **The exact mechanism of felbamate action is unknown. Felbamate blocks voltage-gated sodium channels. It is thought that it antagonizes the NMDA receptor by binding to a glycine recognition site and lowers voltage-gated calcium currents.**
3. Felbamate shows linear pharmacokinetics with a half-life of 20-23 hours in the absence of enzyme-inducing AEDs. Felbamate is hydrolysed by esterase to 2-phenyl-1,3-propanediol monocarbamate, which is next oxidized by aldehyde dehydrogenase to its major metabolite, 3-carbamoyl-2-phenylpropionic acid.
   It was indicated that the intermediate product of that reaction is a reactive metabolite, 3-carbamoyl-2-phenylpropionaldehyde, which undergoes spontaneous elimination to another reactive intermediate, 2-phenylpropenal.
   It is suggested that 2-phenylpropenal (atropaldehyde) reacts rapidly with thiol nucleophiles, such as glutathione, to form mercaptopurates.
   This reaction appears to be responsible for the toxicity of felbamate. Approximately 50% of an oral dose of felbamate is eliminated as unchanged drug.

Felbamate increases phenytoin and valproate serum levels but decreases the level of carbamazepine.

The main adverse effects associated with felbamate therapy include:

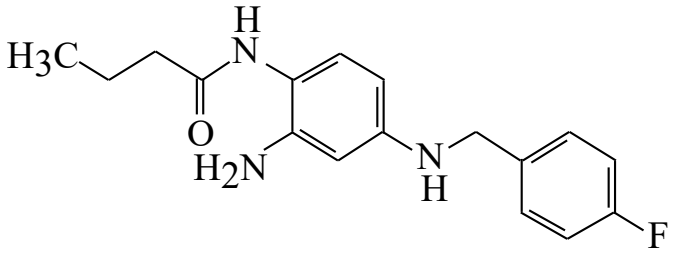
- aplastic anemia (rarely), leading to death in 30% of patients
- severe hepatotoxicity caused by the reactive metabolites of felbamate
- CNS disturbance – exhaustion, vertigo and headache, ataxia, sleep disturbance.

Before the initiation of therapy with felbamate and every two weeks blood and liver functions must be checked.

More recently, a fluorine analogue of felbamate was synthesised, which is presently undergoing drug development, The replacement of the hydrogen atom of the propane chain with fluorine prevents the formation of atropaldehyde.

Potassium channel modulators

Retigabine



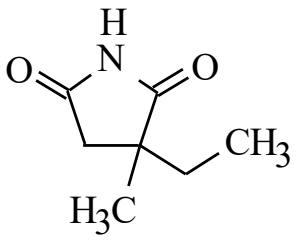
Mechanism of action. Retigabine involves opening of neuronal voltage-activated K^+ channels that serves to stabilize the membrane potential and to control neuronal excitability.

Thus, retigabine also may prove to be useful in the treatment of other diseases associated with neuronal hyperexcitability.

Calcium channel inhibitors
etosuximide and valproate (T-type)
gabapentin and pregabalin (L-type)

Imides. In therapy of epilepsy the following are used:

- **Ethosuximide**, which is the drug of choice for the treatment of simple absence seizures, is not effective against partial complex or tonic-clonic seizures and may increase the frequency of grand mal attacks.
- **Methsuximide**, which is less commonly used than ethosuximide, may be indicated for the control of absence seizures resistant to other drugs. Methsuximide is often combined with phenytoin or phenobarbital when absence seizures coexist with tonic-clonic symptoms.
- **Phensuximide** is occasionally used for the treatment of absence seizures resistant to other drugs, although it is less effective than ethosuximide.



Ethosuximide, RONTON, SUXINUTIN, ZARONTIN

3-Ethyl-3-methylpyrrolidine-2,5-dion

The mechanism of action of the imides occurs due to inhibition of calcium channels of type T, voltage-dependent, especially in the colliculus-cortical neurons.

The bioavailability of ethosuximide is complete (100% of the dose). Its maximal concentration is achieved 3 hours after a single dose. Approximately 20% of the dose is excreted in the urine as unchanged drug and the remainder is metabolized.

The main metabolites are inactive 3-(1-hydroxy)ethyl (~40%) and 3-(2-hydroxy)ethyl derivatives (~15%), which are excreted as glucuronides. The half-time of elimination is 40–50 hours in adults and approx. 30 h in children.

Ethosuximide is the least toxic of the succinimides. However, it can cause

- gastrointestinal disturbance (irritation of the stomach, nausea, vomiting may occur on chronic administration),
- dose-related CNS effects such as drowsiness, lethargy, dizziness, ataxia, sleep disturbance, inability to concentrate and depression
- in sensitive individuals, idiosyncratic reactions include Stevens-Johnson syndrome or urticaria, leukopenia, aplastic anemia, thrombocytopenia, systemic lupus erythematosus and parkinsonian-like symptoms.

Methsuximide and phensuximide are more toxic than ethosuximide.

Modulators of ligand dependent ionic channels

Benzodiazepines

The benzodiazepines are widely used as sedative-hypnotics and anxiety drugs.

In therapy of seizures the following benzodiazepines are effective: diazepam, lorazepam, clonazepam, clorazepate dipotassium and midazolam.
The duration of action is short for diazepam (2 hours) and midazolam (3-4 hours), longer for clonazepam (24 hours) and much longer for lorazepam (up to 72 hours) but it is not correlated with the plasma concentration-time profiles for these drugs.

The benzodiazepines, similarly to phenobarbital, produce their antiseizure effects mainly by enhancing the effect of the inhibitory neurotransmitter GABA on the GABA-A chloride channel.

Additionaly, it is believed that the benzodiazepines may diminish voltage-dependent sodium, potassium and calcium currents in a manner independent of the $GABA_A$ receptor complex.

The benzodiazepines, after oral administration, are well absorbed and achieve maximal concentration in plasma after 1–4 hours. Their binding with proteins is correlated with their lipophilicity and ranges from 95% (diazepam) to 85% (clonazepam).

The benzodiazepines only in small amounts are eliminated in the urine as unchanged drugs.
They are metabolized to active 3-hydroxy derivatives and N-demethyl derivatives (diazepam).

The 7-nitro derivatives (nitrazepam and clonazepam) are reduced to inactive amino derivatives. Half-time for diazepam is 24–48 hours, for clonazepam approx. 24 hours, for lorazepam – approx. 14 hours.

Barbituric acid and hexahydropyrimidinedione derivatives

Action and application. Many barbiturates show sedative-hypnotic activity (Ch. 12.3) and only a few have antiseizure properties. Paradoxically, many barbiturates cause convulsions at larger doses.

The barbiturates clinically useful as AEDs are phenobarbital and mephobarbital. Phenobarbital is indicated for the treatment of partial and generalized tonic-clonic seizures in all age groups, although it is less effective than phenytoin and carbamazepine in adults. It is the drug of choice for seizures in infants up to 2 months old.

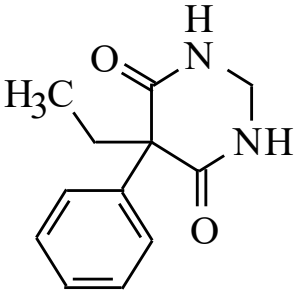
Mephobarbital (PROMINAL), like phenobarbital, is classified as long-acting barbiturate. It is less commonly used in the treatment of generalized and partial seizures than phenobarbital.

The mechanism of action. The mechanism of the antiseizure action of the barbiturates is unknown, but it is believed that they block sodium channels and enhance GABA-mediated inhibitory transmission.

Pharmacokinetics. The absorption of phenobarbital from the GI tract is slow but nearly complete and shows linear kinetics. Phenobarbital is 40–60% protein-bound and shows a long half-life of 2–6 days (shorter in children), which shows big individual differences. Approx. 25–50% of the dose is eliminated in the urine as unchanged drug. The remainder is metabolized by hydroxylation to an inactive metabolite (5-*p*-hydroxyphenobarbital), which is conjugated with UDPGA or PAPS. Glucuronide and sulfate are excreted in the urine.

Phenobarbital is a potent liver enzyme-inducing drug of CYP3A4 and because of that it increases the ability of the liver to metabolize many drugs when taken concurrently that are normally metabolized by CYP3A4.
It also induces UDP-glucuronyltransferase. Because of that phenobarbital decreases plasma levels of carbamazepine, valproate, lamotrigine, tiagabine, zonisamide, theophylline, cimetidine and other drugs. Serum concentrations of phenobarbital are increased by valproate.
Approximately 50% of an oral dose of mephobarbital is absorbed from the GI tract. About 50% of a single oral dose of mephobarbital is converted to phenobarbital.

The adverse effects. Sedation, ataxia, nystagmus, vertigo and acute psychotic reactions may occur with chronic use. Nausea, vomiting and morbilliform rash are observed in sensitive individuals. Agitation and confusion occur at high doses.



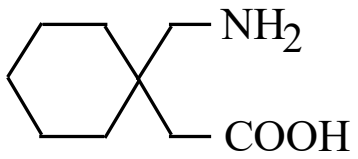
Primidone, MIZODIN

5-Ethyl-5-phenylhexahydropyrimidine-4,6-dione

Primidone is the 2-deoxy derivative of phenobarbital. It is used for initial or adjunctive treatment of simple partial, complex partial and tonic-clonic seizures. Primidone is less effective against these types of seizures than phenytoin or carbamazepine and shares the antiseizure and sedative actions of phenobarbital. Primidone is also used in trigeminal neuralgia and in primary neuralgia.

60–80% of an oral dose of primidone is absorbed from the GI tract.
A maximal concentration of primidone in plasma is achieved after aprox. 4 hours. Primidone is metabolized to active metabolites – phenobarbital (15–25% of the dose) and phenylethylmalonamide (50–70% of the dose; more toxic than primidone). These metabolites accumulate in the body. The half-life of primidone is 5–15 hours. At primidone concentrations greater than 10 μg/ml of plasma toxic effects can appear.
The adverse effects during therapy with primidone are similar to those observed when phenobarbital is used.

GABA transporter inhibitors: gabapentin, tiagabine

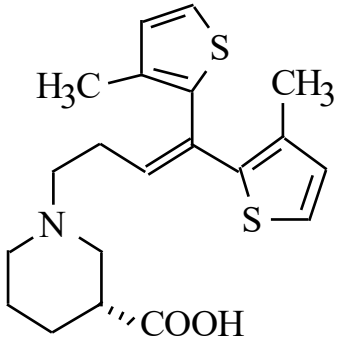


Gabapentin, NEURONTIN
1-Aminomethyl-1-carboxymethylcyclohexan

Gabapentin is indicated as an adjunct for use against partial seizures with or without secondary generalization, in patients more than 12 years of age.

Gabapentin, in contrast to GABA, crosses the blood-brain barrier. Its absorption and distribution into the CNS appears to be dependent on the amino acid transporter.
The mechanism of action. Gabapentin binds to the GABA transporter GAT1, blocking the uptake of GABA into both neurons and glia, enhancing GABA-mediated inhibition in this way.
Gabapentin exhibits linear pharmacokinetics.

The therapeutic concentration of gabapentin in plasma is 2–5 μg/ml. Its elimination half-time is 5-7 h.
The adverse effects of gabapentin are not serious. CNS effects include mild to moderate sedation, fatigue, ataxia, headache, dizziness and diplopia. Gabapentin dosage may need to be decreased in patients with renal disease and in the elderly.



Tiagabine, GABITRIL

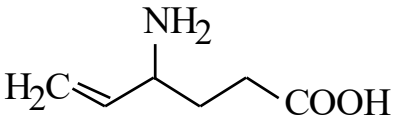
(*R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidin-3-carboxylic acid

Tiagabine (a nipecotic acid derivative) is indicated for adjunctive use in epileptic patients more than 12 years of age with partial seizures which are not controlled by first-line drugs. Tiagabine binds to the GABA transporter GAT1, blocking the uptake of GABA into both neurons and glia, enhancing GABA-mediated inhibition in this way.

Tiagabine is well absorbed from the GI tract (90-95% bioavailability) and shows linear pharmacokinetics with a plasma half-life of 5-8 hours, which makes it necessary to administer it several times daily. It is metabolized by CYP3A4, then the product of oxidation is conjugated with UDPGA.

Enzyme-inducing AEDs (carbamazepine, phenytoin and barbiturates) change lamotrigine pharmacokinetics. Valproate decreases the protein binding of tiagabine, increasing its plasma concentration in patients receiving these drugs together.
The adverse effects during therapy with tiagabine are more common than with other adjunctive drugs and most often involve the CNS. They include somnolence, tremor, headache, dizziness, abnormal thinking, depression, and psychosis. Additionaly diarhea and skin blood extravasation can appear.
Tiagabine is contraindicated in serious hepatic diseases.

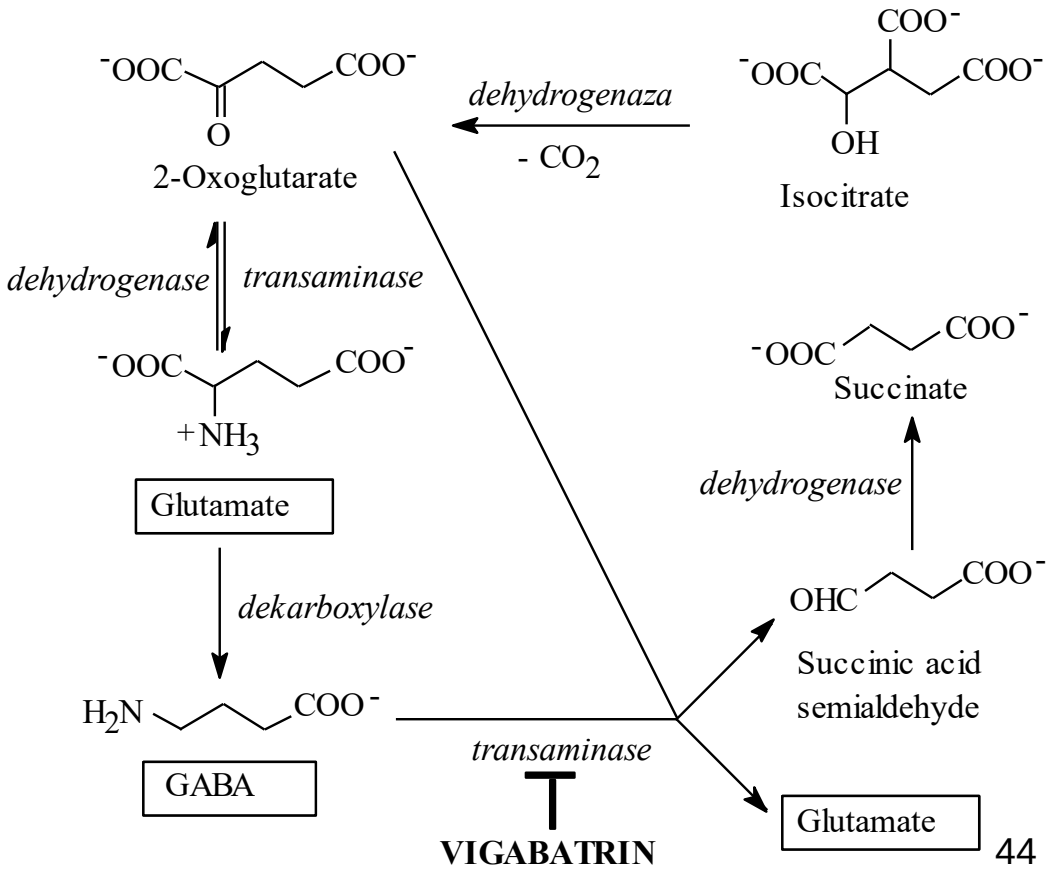
GABA-aminotransferase inhibitors: vigabatrin



Vigabatrin, SABRIL; 4-Amino-5-hexenoic acid

Vigabatrin increases the GABA concentration in the brain by an irreversible blockade of GABA-amino-transferase.
This enzyme is responsible for the transformation of GABA to succinic acid semialdehyde and glutamate.

Vigabatrin bonds covalently with the active site of the enzyme.

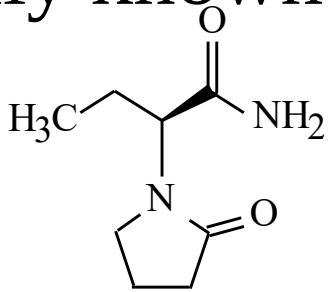


Pharmacological activity is demonstrated by the *S*-enantiomer of vigabatrin.
In monotherapy of epilepsy vigabatrin shows similar action to carbamazepine.
It is used in the treatment of epilepsy resistant to other AEDs.

The absorption of vigabatrin after oral administration is rapid and almost complete.
A maximal concentration in plasma is achieved after approx. 2 h. Its total bioavailability is 70–80%. Vigabatrin is eliminated in the urine as unchanged drug. Its half-time of elimination is 5–7 h.

During therapy with vigabatrin the following adverse effects may appear: fatigue, somnolence, headache, vertigo, tachyphasia, aggression, vision disturbance and gastrointestinal disturbance.

AEDs which mechanism of action is not fully known



Levetiracetam, KEPPRA

(*S*)-α-ethyl-2-oxo-pyrrolidin-1-acetamide

Levetiracetam (*S*-enantiomer of etiracetam) is indicated as an adjunct in the treatment of partial onset seizures in adults. Its mechanism of action is unknown.

Levetiracetam is rapidly and completely absorbed from the GI tract.

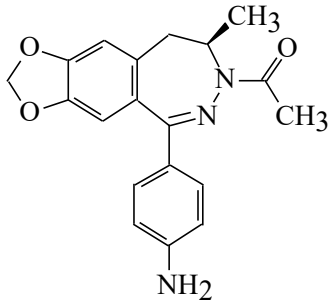
It exhibits linear pharmacokinetics with an elimination half-time in adults of approx. 7 hours.

It is esterase-hydrolyzed to its carboxylic acid metabolite, which is not affected by the hepatic metabolizing enzymes (CYP450, UGT or epoxide hydrolase).

The adverse effects of levetiracetam include mild to moderate somnolence, asthenia, ataxia and dizziness.

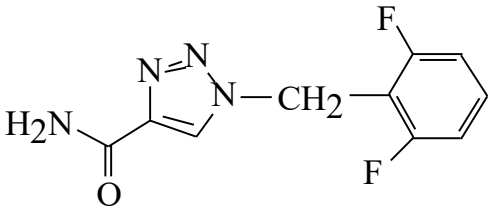
Its use in the elderly or in patients with renal impairment will require an individualized dose and an additional dose is needed after renal dialysis.

Antiepileptic drugs in phase III clinical trials



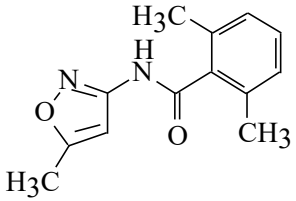
Talampanel, benzodiazepine derivative

AMPA/KA receptor antagonist



Rufinamide,
1,2,3-triazol carboxamide derivative

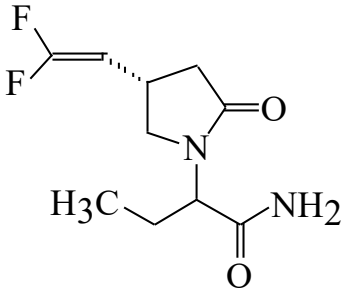
Blocks sodium channels



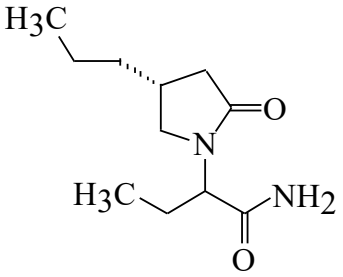
Soretolide for treatment of myoclonic seizures.

It has a mechanism of action similar to that of carbamazepine.

Antiepileptic drugs in phase III clinical trials (2)



Seletracetam



Brivaracetam

S-(–)-Leveritacetam derivatives for treatment of myoclonic seizures.

Problems

Theoretically, the ideal AED should among other things, completely supress seizures in doses that do not cause sedation or other undesired CNS toxicity.

The AED should be well tolerated and highly effective against various types of seizures and be devoid of undesirable side effects on vital organs and functions.

Its onset of action should be rapid after parenteral injection for control of status epilepticus and it should have a long duration of effect after oral administration for prevention of reccurent seizures.

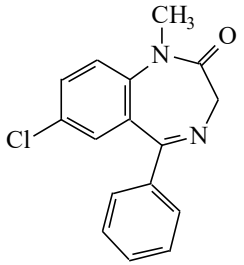
Choose the correct answers.

a) Carbamazepine and oxcarbazepine are iminostilbene derivatives.
b) Etosuximide and valproate are calcium channel inhibitors.
c) Topiramate is NMDA Ca^{2+} channel modulator.
d) Felbamate is AMPA/KA Ca^{2+} channel modulator.
e) Gabapentin and tiagabine are GABA-aminotransferase inhibitors.

The correct are: 1) a, and c; 2) c, d and e; 3) b and c; 4) a, c and d; 5) a and b

Which of the following formulas is correct for

a) Vigabatrin
b) Carbamazepine
c) Primidone
d) Phenytoin
e) Diazepam
f) Phenobarbital



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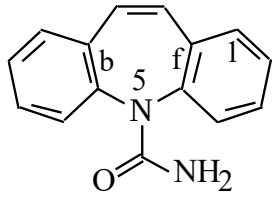

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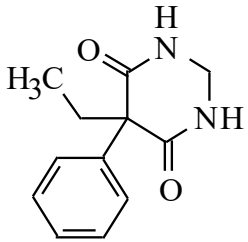

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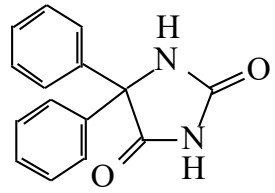

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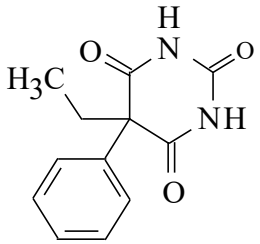

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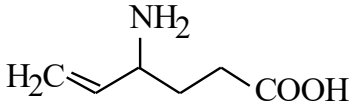

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