# Pharmaceutical Chemistry

## Anticonvulsant Drugs

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# Anticonvulsant Drugs (AEDs):

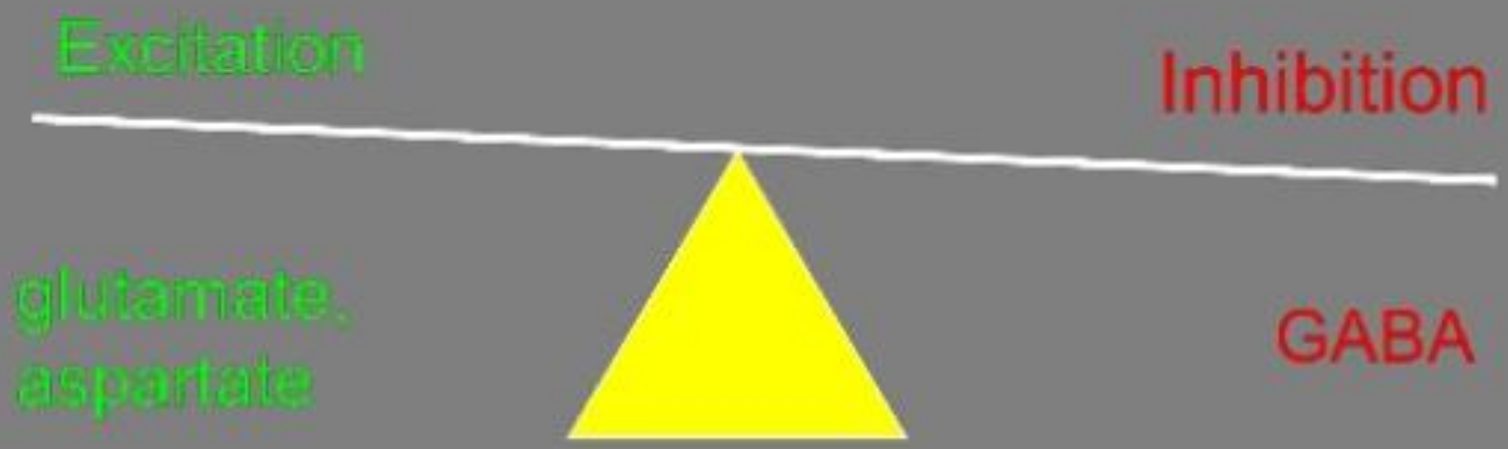
Epilepsy is not a disease. It is the most prevalent neurological disorder affecting more than 0.5% of the world's population. It is characterized by recurrent seizures.

Seizures, on the other hand, are symptoms of disturbed electrical activity in the brain characterized by episodes of abnormal, excessive, and synchronous discharge of a group of neurons within the brain that cause involuntary movement, sensation, or thought.

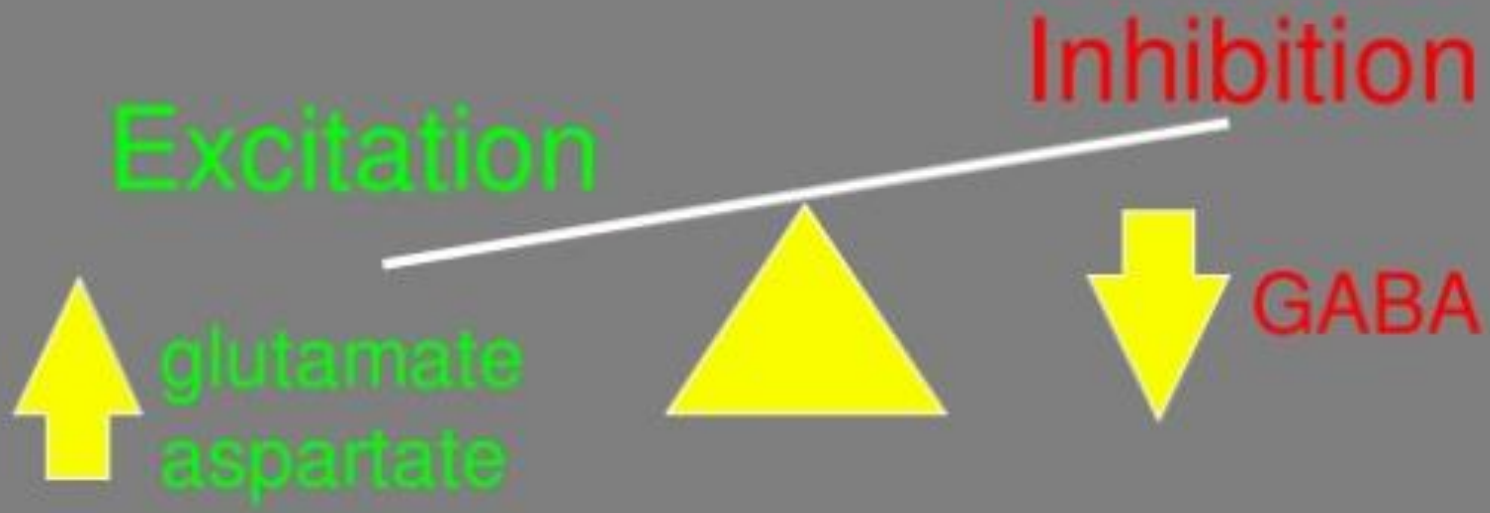
It is generally agreed that seizures may result from primary or acquired neurological disturbances of brain function as a result of an imbalance between excitatory and inhibitory processes in the brain.

There are many possible causes of seizure including brain tumors or infections, head trauma, neurological diseases, systemic or metabolic disorders, alcohol abuse, drug overdose, or toxicities.

# Normal CNS Function



# Hyperexcitability reflects both increased excitation and decreased inhibition



# Classification of Epileptic Seizures and Recommended Initial Drug Therapy

Seizures are classified, based on their initial signs and symptoms and the pattern seen on the electro-encephalogram (EEG), into two broad categories:

**Primary generalized seizures**

Two major types of generalized seizures are the primarily generalized tonic–clonic seizures (grand mal) and the absence (petit mal) seizures.

**Partial seizures**

Major types of partial seizure are simple partial seizures (focal) and complex partial seizures (temporal lobe or psychomotor).

# Mechanisms of action of anticonvulsants

(A) Modulation of voltage-gated ion channels (Na, $Ca_2$, and K).

(B) Enhancement of γ- amino butyric acid ($GABA$)-mediated inhibitory neurotransmission.

(C) Attenuation of excitatory (particularly glutamate-mediated) neurotransmission in the brain.

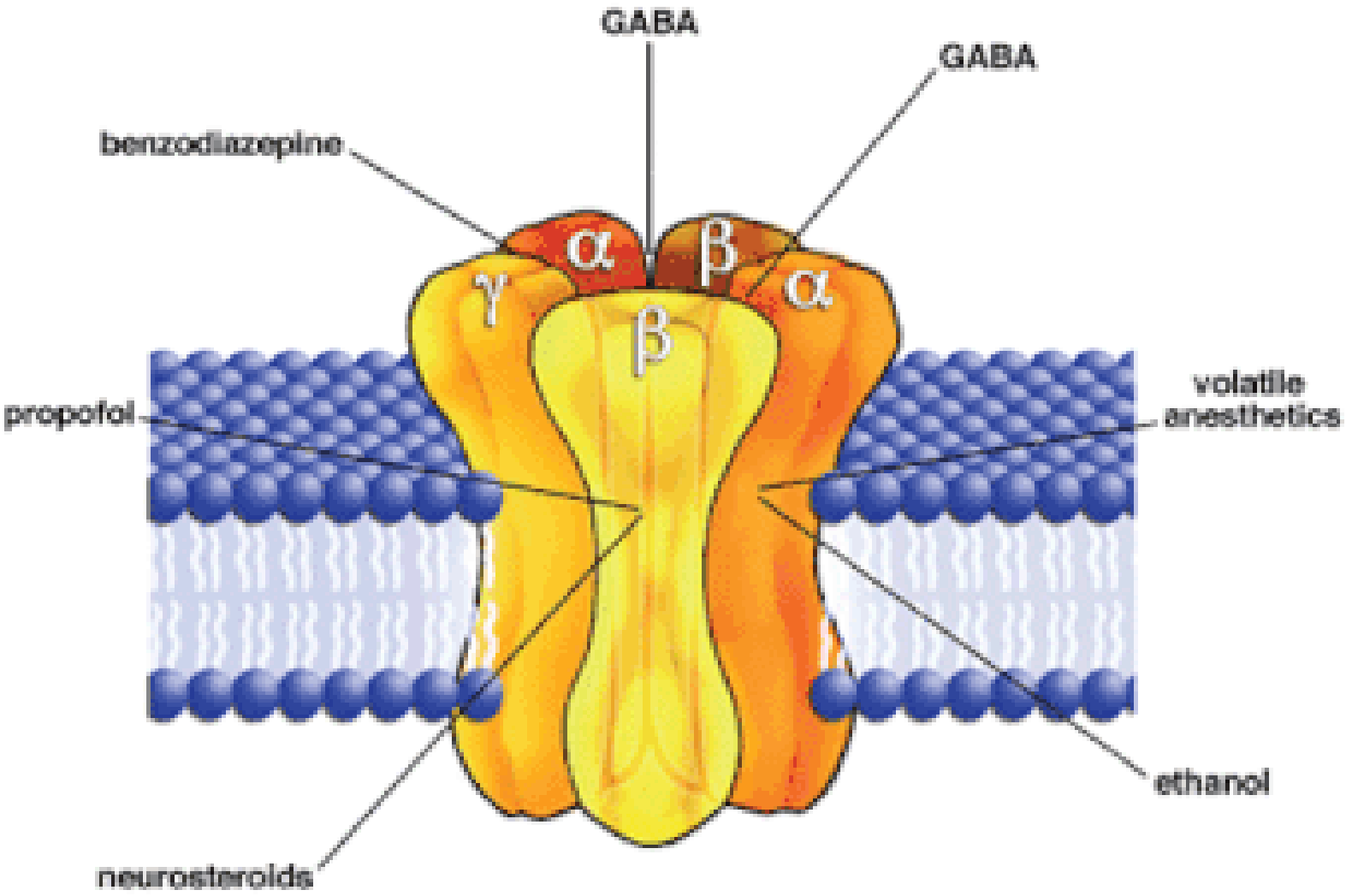
Many of AEDs, especially the newer drugs, work by more than one of the above mechanisms of actions, therefore possessing a broader spectrum of antiepileptic action.

# GABA A Receptors as Target for Anticonvulsant

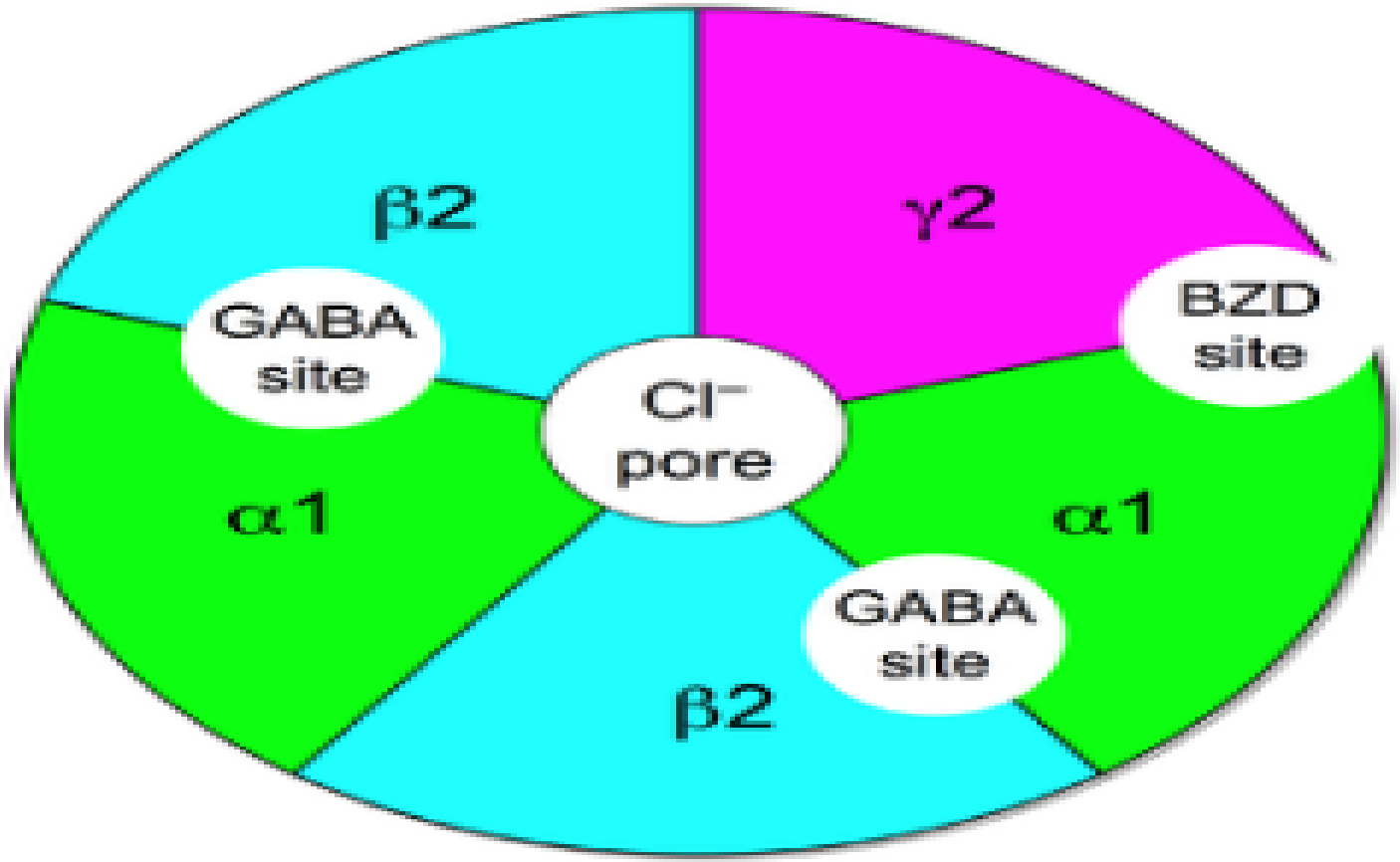
It is now well recognized that cellular excitability leading to convulsive seizures can be attenuated by GABA ergic stimulation in the brain.

The $GABA_A$ receptor is one of two ligand-gated ion channels responsible for mediating the effects of $GABA_A$, the major inhibitory neurotransmitter in the brain.

Activation of the $GABA_A$/benzodiazepine (BZD) receptors/chloride channel complex allows increased chloride conductance, thereby preventing the spread of neuronal excitations.




$GABA_A$ receptor and where various ligands bind.




Schematic diagram of a $GABA_A$ receptor protein ($(\alpha1)_2(\beta2)_2(\gamma2)$) which illustrates the five combined subunits that form the protein, the chloride ($Cl^-$) ion channel pore, the two GABA active binding sites at the α1 and β2 interfaces, and the benzodiazepine (BDZ) allosteric binding site[1]

The potential targets for AED's action on the GABA ergic inhibitory synapses include:

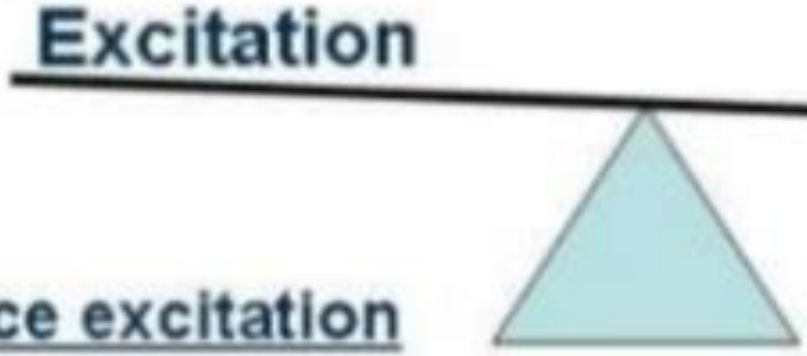
(a)Drugs that enhance the biosynthesis of GABA (gabapentin, pregabalin, and VPA)

(b) Drugs that inhibit GABA degradation (vigabatrin).

(c) Drugs that inhibit the reuptake of GABA (tiagabine)

(d) Drugs that bind to an allosteric site on the postsynaptic $GABA_A$ receptor complex that increase chloride conductance (barbiturates, BZDs).

# AEDs Act by Restoring Balance




## Reduce excitation

* Phenytoin (PHT)
* Carbamazepine (CBZ)
* Valproic acid (VPA)
  Felbamate (FBM)
  Lamotrigine (LTG)
-> Topiramate (TPM)
  Oxcarbazepine (OXC)
  Zonisamide (ZNS)
  Levetiracetam (LEV)

## Increase inhibition

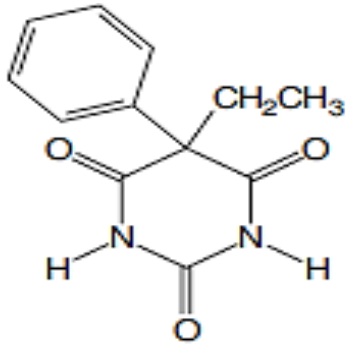
* Phenobarbital (PB)
* Benzodiazepines (BDZ)
  Tiagabine (TGB)
* Vigabatrin (VGB)
  Valproate (VPA)
  Felbamate (FBM)
-> Topiramate (TPM)
  Zonisamide (ZNS)

# Phenobarbital and Primidone (Mysoline)

Barbiturate anticonvulsants are a group of drugs derived from barbituric acid and they act by suppressing activity of the central nervous system.

Barbiturate anticonvulsants enhance the action of GABA, which is an inhibitory neurotransmitter, and inhibits initiation of discharge that would start the seizure.

Barbiturates facilitate GABA-mediated opening of chloride channels and increases effectiveness of GABA. Although sedative–hypnotic barbiturates commonly display anticonvulsant properties, only phenobarbital display enough anticonvulsant selectivity for use as antiepileptics. Barbiturates act as positive allosteric modulators and, at higher doses, as agonists of $GABA_A$ receptors.




Phenobarbital

Barbiturates bind to the GABAA receptor at multiple homologous transmembrane pockets located at subunit interfaces, which are binding sites distinct from GABA itself and also distinct from the benzodiazepine binding site.

Like benzodiazepines, barbiturates potentiate the effect of GABA at this receptor.

Barbiturates produce their pharmacological effects by increasing the duration of chloride ion channel opening at the GABAA receptor .(This increases the efficacy of GABA), whereas benzodiazepines increase the frequency of the chloride ion channel opening at the GABAA receptor. (This increases the potency of GABA). The direct gating or opening of the chloride ion channel is the reason for the increased toxicity of barbiturates compared to benzodiazepines in over dose.

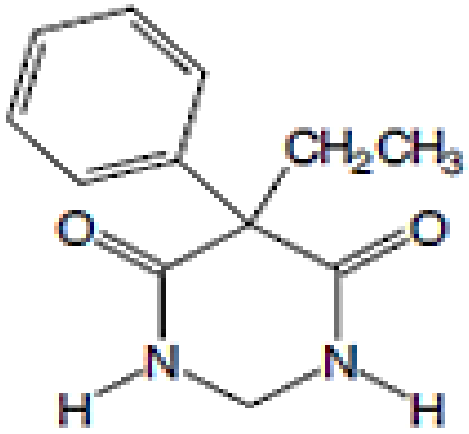
# Primidone (Mysoline)

Is metabolized by CPY2C9/19 to phenobarbital and phenylethylmalonamide (PEMA)

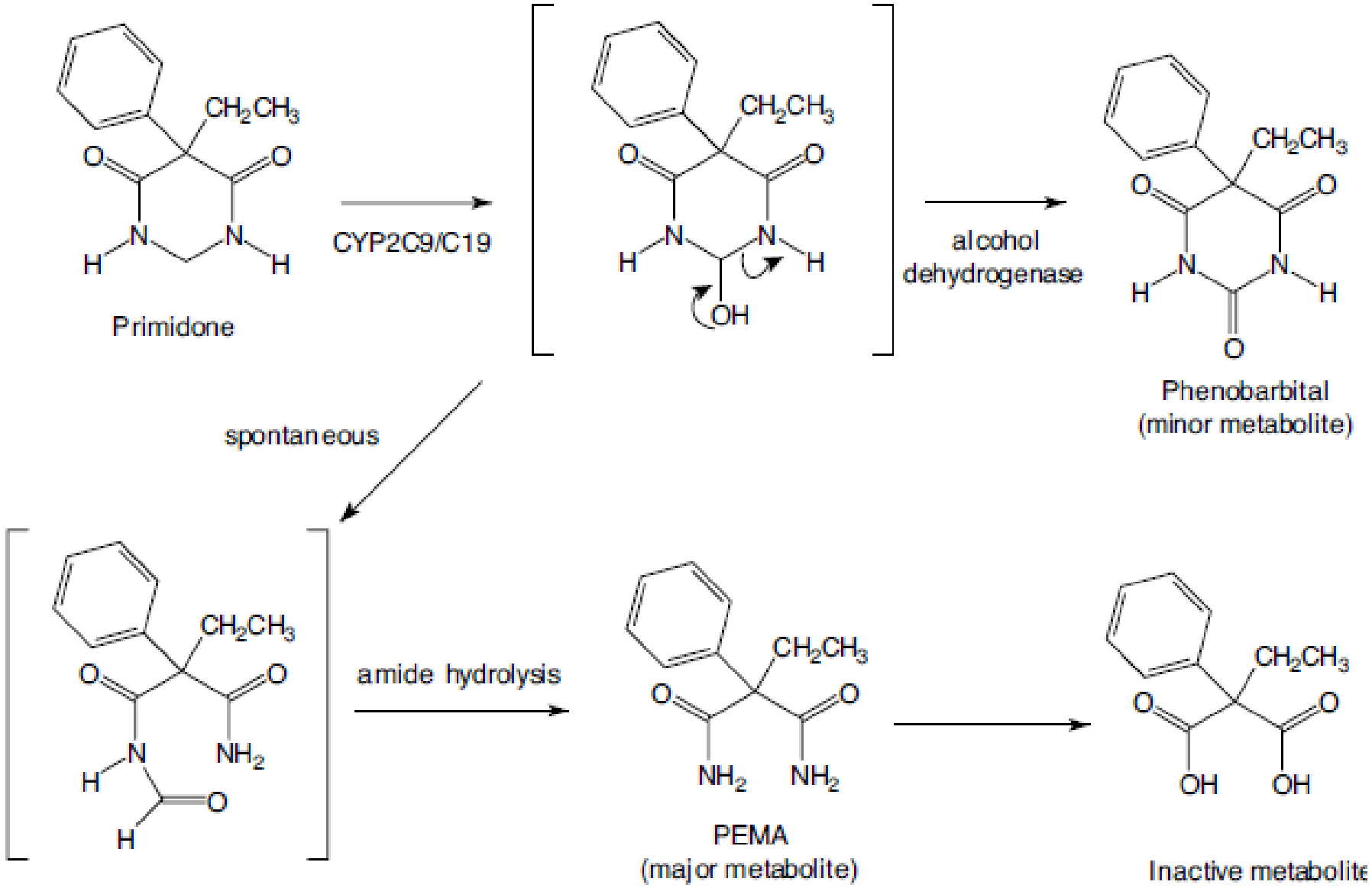
Both of these metabolites have anticonvulsant activities.

However, it is generally believed that the pharmacological action of primidone is mainly a result of the minor metabolite, phenobarbital.

Thus, primidone is much less potent/toxic than phenobarbital, because most of the drug is rapidly degraded to the less potent metabolite, PEMA.




Primidone




Metabolic biotransformation of primidone.

# Voltage-Gated Ion Channels as Targets for Anticonvulsants

- Voltage-gated sodium channels (VGSCs) in the presynaptic nerve terminal of the excitatory glutamate receptors are the molecular target for phenytoin, CBZ, and lamotrigine as well as some of the newer AEDs, such as OXC, felbamate (FBM), and zonisamide. These aromatic AEDs inhibit excessive neuronal firing by binding to a site near the inactivation gate, thereby prolonging inactivation of VGSCs.
- The voltage-gated calcium channels (VGCCs) are essential in regulating $Ca_2$ signaling, which is associated with many important cellular events such as the release of excitatory glutamate neurotransmitters, the plasticity changes of long-term potentiation in learning and memory, and the maintenance of homeostasis of nerve cells. It has been suggested that excessive influx of $Ca_2$ plays a critical role in the induction and progression of epileptic seizures

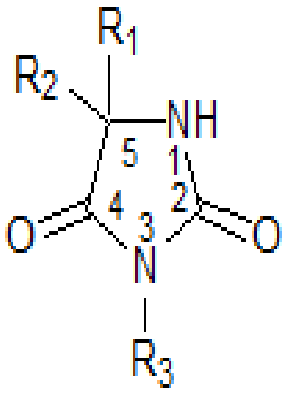
## ➢ Voltage-gated potassium channels

Potentiation of the voltage-gated K channels is another attractive target for designing of newer AEDs, because they are intimately associated with the membrane repolarization processes.

Levetiracetam (LEV), a novel AED recently marketed for the adjunctive therapy of refractory partial seizures in adults, has been suggested to work by reducing the voltage-operated

A-type potassium currents as one of its mechanism of actions

# Hydantoins




**Hydantoins**

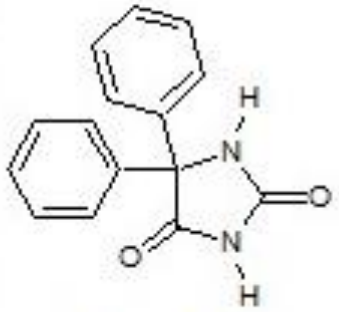
1. Close structural relatives of barbiturates
2. Only lacking the 6-oxo group and are cyclic monoacylureas rather than diacylureas
3. As a consequence of losing a carbonyl group weaker organic acids than barbiturates and thus their sodium salt (e.g., phenytoin sodium) generates stronger alkaline solution

## SAR of Hydantoins

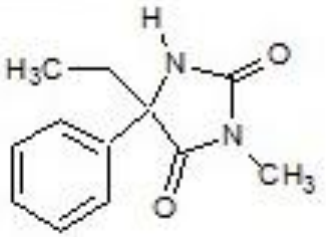
Most of the clinically used drugs in this class possess bulky aromatic ring in position $C^5$ that confers usefulness in generalized seizures, partial seizures and status epilepticus but not well for absence seizures

# Hydantoin Drugs

Phenytoin is metabolized by *p*-hydroxylation followed by conjugation similar to Phenobarbital. Mephenytoin is the hydantoin analogue of mephobarbital which is also a prodrug, converted into the dealkylated derivative. Metabolism is also by *p*-hydroxylation and then glucuronidation

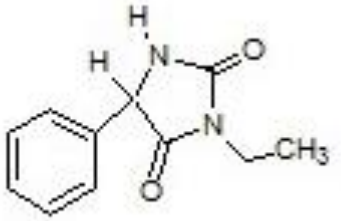


**Phenytoin**



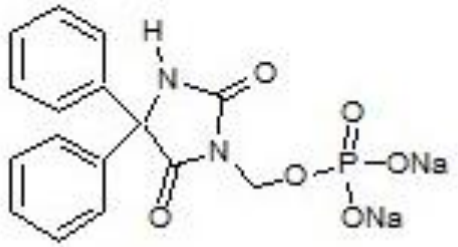
**Mephenytoin**

Ethotoin is dealkylated to the active drug. In this case there is free hydrogen at $C_5$, which explains its very low potency. Metabolism is also by *p*-hydroxylation and then glucuronidation

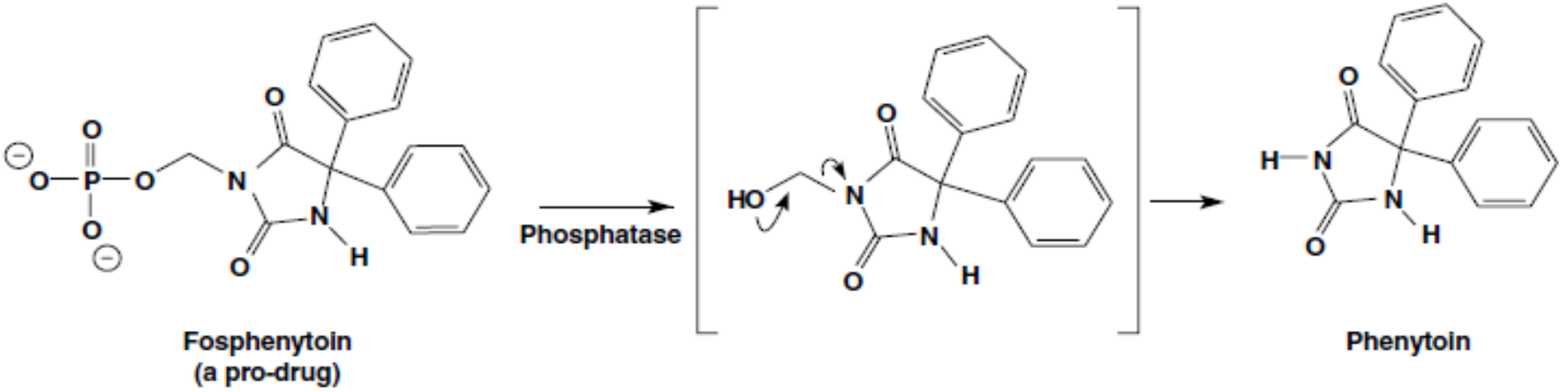


**Ethotoin**

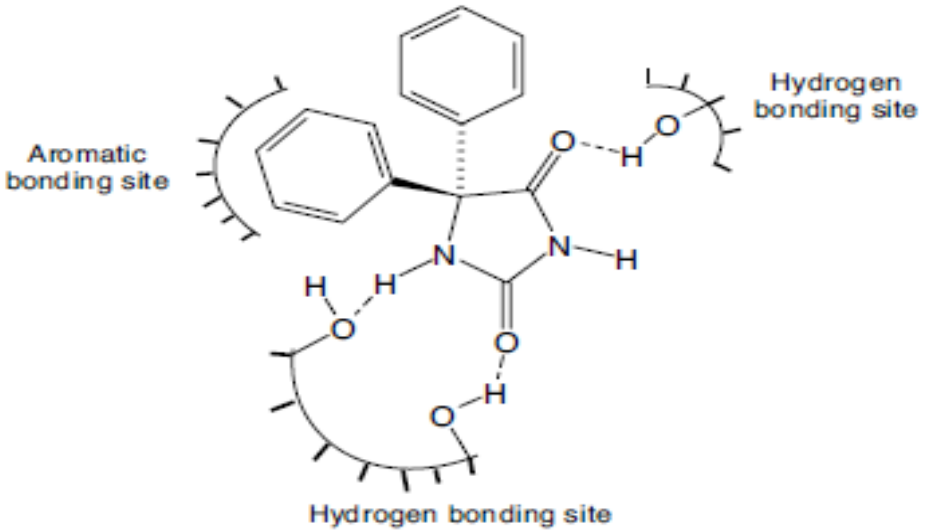
Fosphenytoin is Phosphate ester of phenytoin, rapidly hydrolyzed to phenytoin *in vivo*. Phenytoin sodium must be buffered to an alkaline pH to maintain solubility, thus is very irritating when injected. Fosphenytoin is neutral (pH~7) so is less irritating



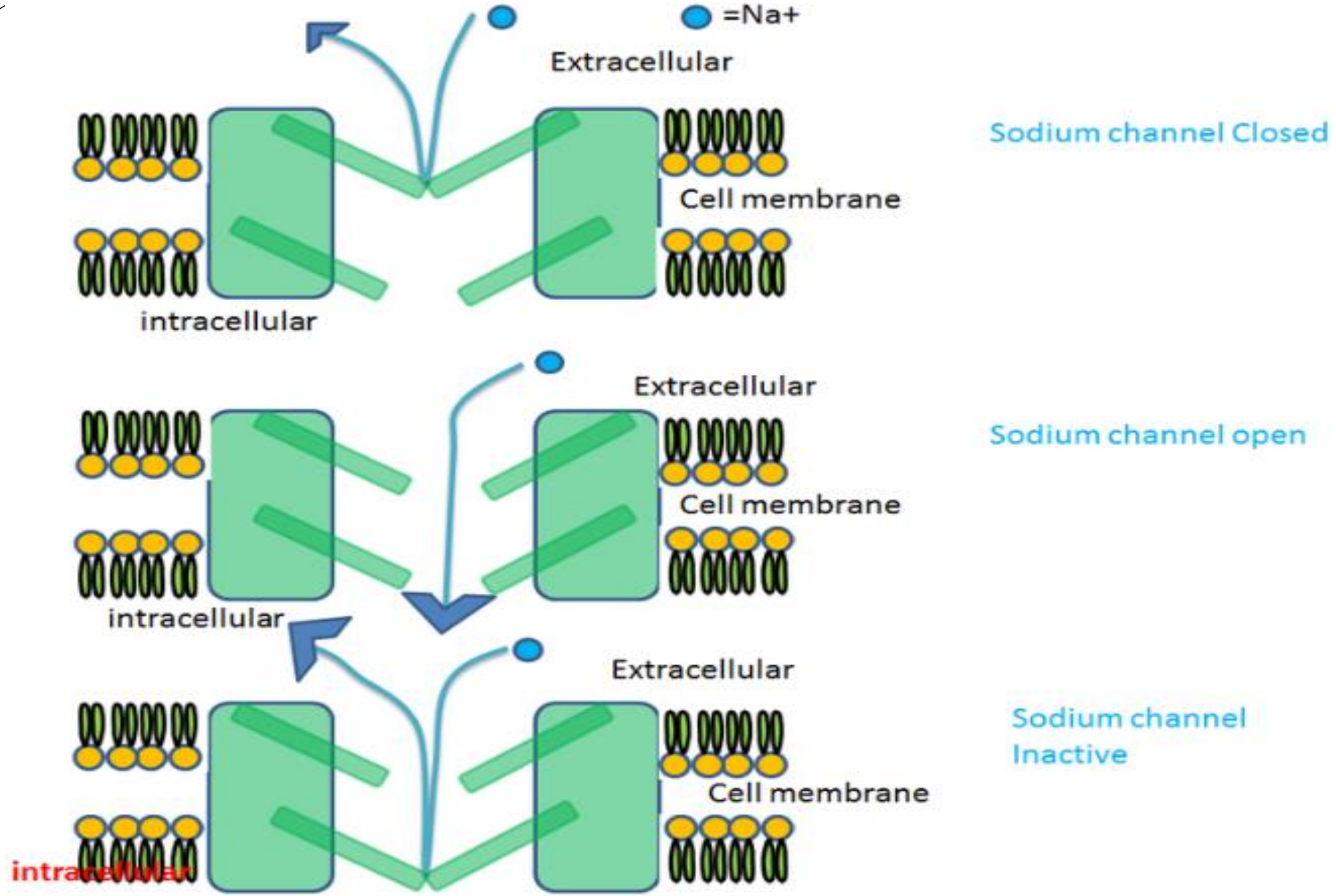
**Fosphenytoin**




Biotransformation of fosphenytoin to phenytoin.

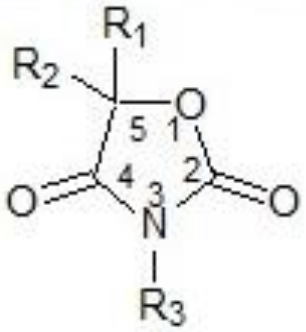



Binding of phenytoin to the hypothetical "inactivation gate" receptor on the voltage-gated sodium channels.




The mechanism of action of phenytoin sodium. Sodium channels are: 1) Closed 2) Open 3) Inactive (phenytoin effect)

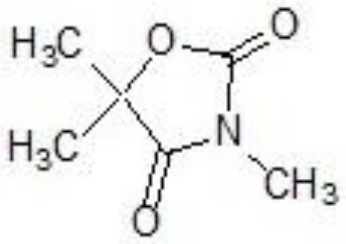
# Oxazolidinediones




**Oxazolidinedione**

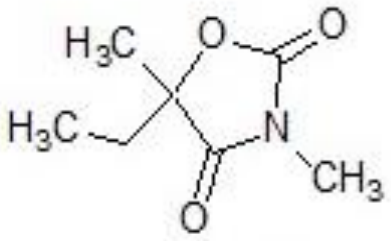
Replacement of the N-H group at position 1 of the hydantoin with an oxygen atom yields the oxazolidine-2,4-dione system

Trimethadione is useful for absence seizures. Note the absence of bulky substituents at the $C_5$ position which are useful in absence seizures. It is metabolized to 5,5 dimethyl oxazolidine 2,4 dione (dimethadione) which is also active. Both trimethadione and dimethadione are excreted in the urine and are very toxic




**Trimethadione**

Paramethadione is also N dealkylated, half life is 12-24 hours. Some excreted by kidney. The metabolite is active and probably accounts for most activity the half life of which is 14 days and is excreted by the kidney. Also it is fairly toxic



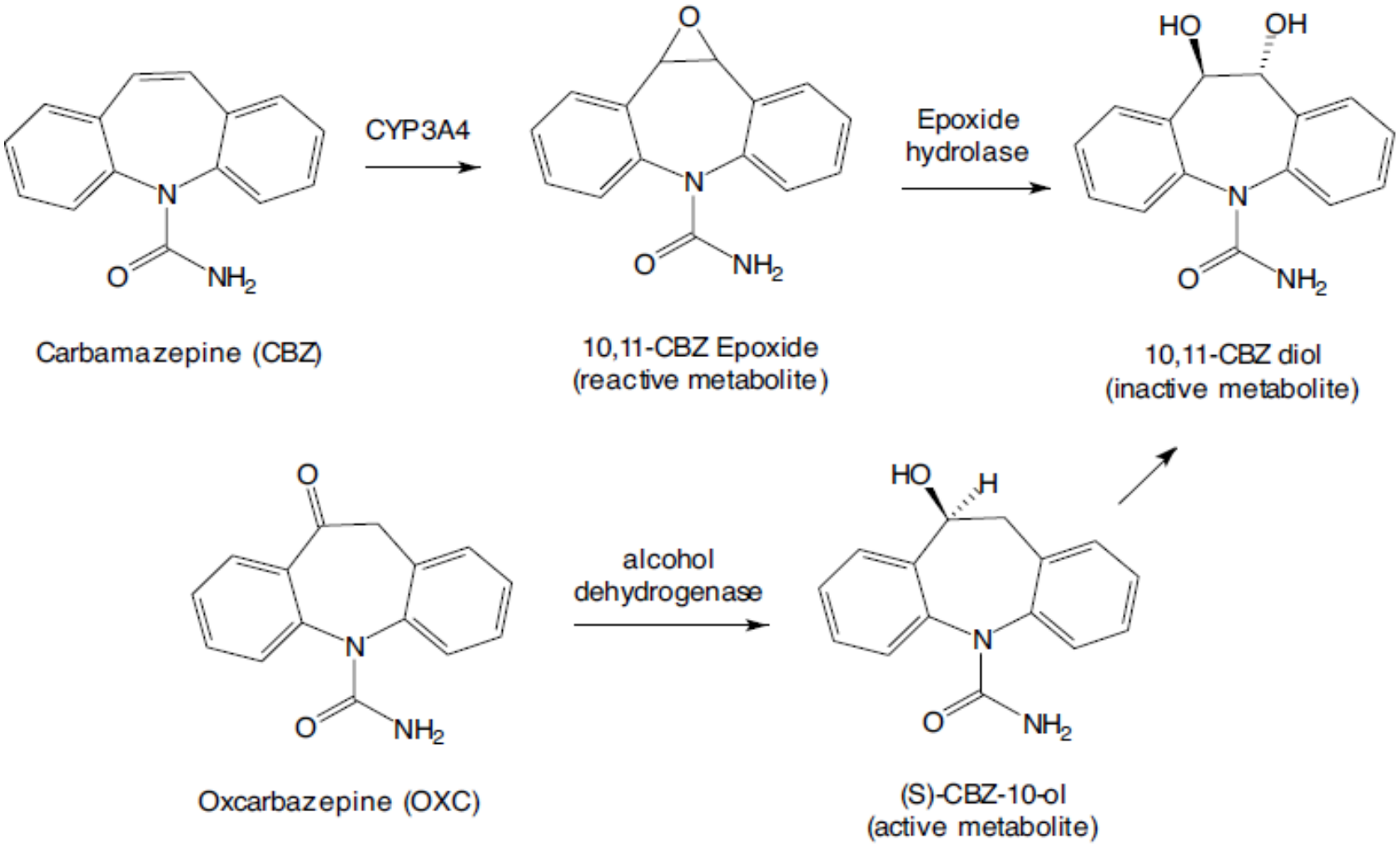

**Paramethadione**

## Carbamazepine (Tegretol)

The two phenyls substituted on the urea nitrogen fit the pharmacophore pattern suggested for binding to the VGSC. Like phenytoin, CBZ is useful in generalized tonic– clonic and partial seizures. Carbamazepine stabilizes the inactivated state of voltage-gated sodium channels, making fewer of these channels available to subsequently open. This leaves the affected cells less excitable until the drug dissociates. Carbamazepine is also a GABA receptor agonist, as it has also been shown to potentiate GABA receptors made up of alpha1, beta2, and gamma2 subunits

**Oxcarbazepine (Trileptal)** (OXC) is a newer AED with a similar mechanism of action to CBZ except for its metabolic inactivation pathway.

# Metabolism of Carbamazepine and Oxcarbazepine



# Drugs that enhance the biosynthesis of GABA

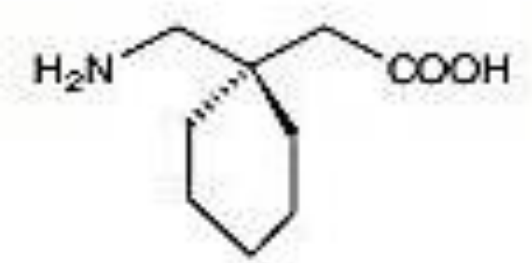
GABA, the major inhibitory neurotransmitter in the brain, is biosynthesized at the GABA ergic neurons by the decarboxylation of the amino acid, L-glutamic acid (itself an excitatory amino acid neurotransmitter in the brain). The essential cofactor for this enzymatic reaction is pyridoxal phosphate (vitamin B6).

The rate-limiting enzyme that catalyzes this conversion is L-glutamic acid decarboxylase (GAD).

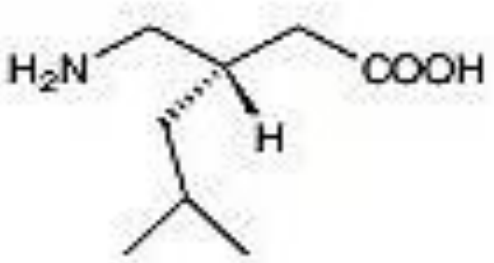
A 3-substituted GABA, gabapentin and especially pregabalin, may have the ability to activate GAD, Both of these drugs are weak activators of GAD.

Gabapentin and its closely related analog pregabalin, (S)-3-isobutyl-GABA are broad-spectrum anti consultants. with multiple mechanisms of action.

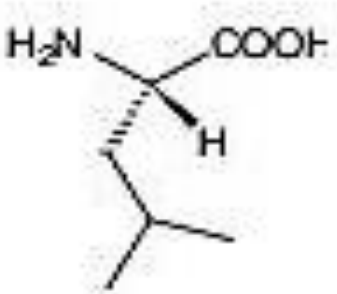
In addition to modulating calcium influx and stimulate GABA biosynthesis, they also compete for the biosynthesis of L-glutamic acid because of their structural similarity to L-leucine.




Gabapentin

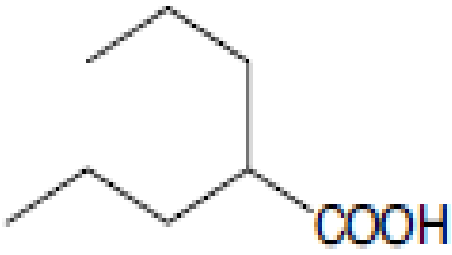



Pregabalin

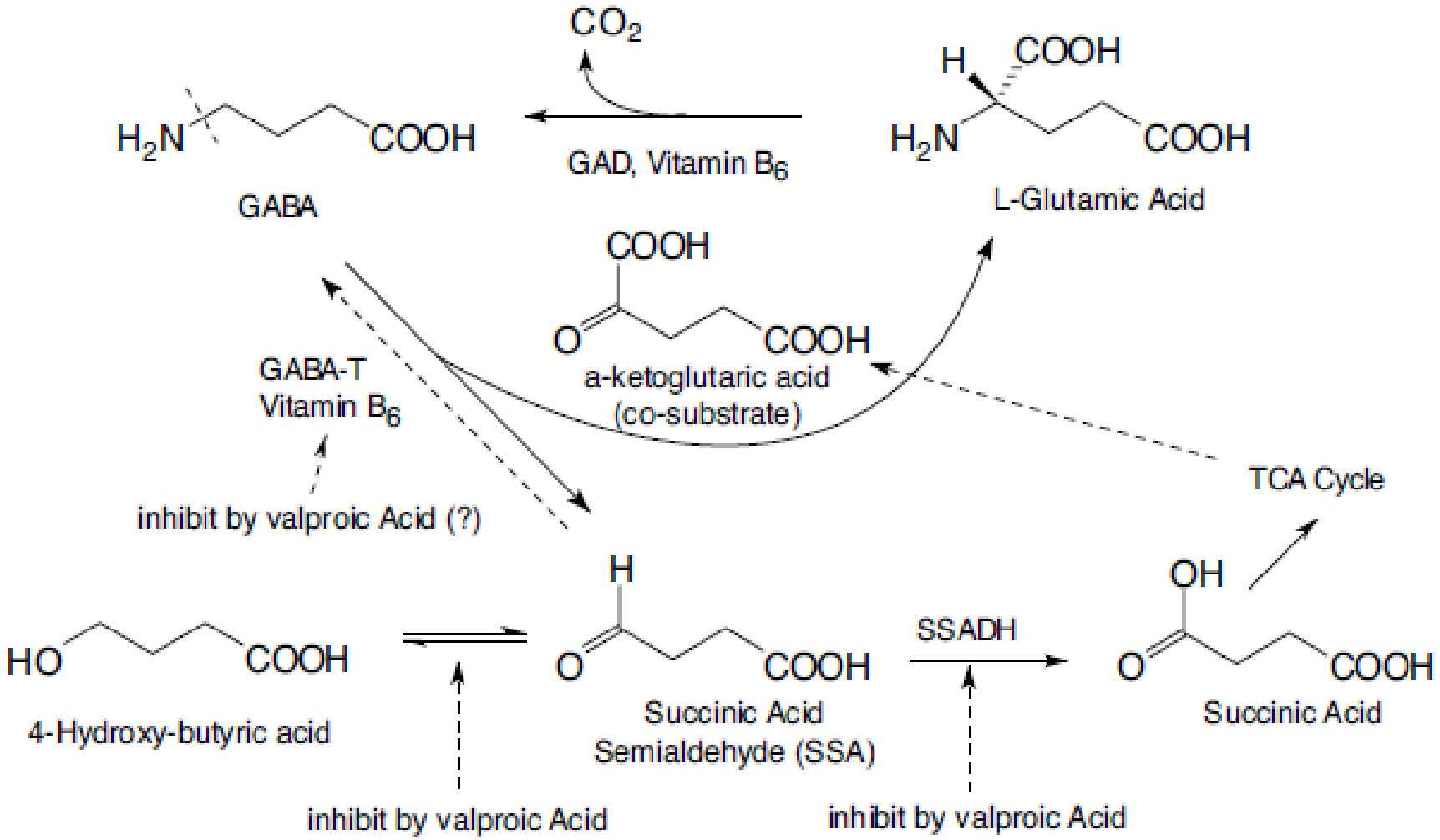



L-Leucine

**Valproic Acids** (VPA), also elevates brain levels of GABA in patients with epilepsy. It is generally agreed that VPA inhibits SSADH, the enzyme responsible for conversion of SSA to succinic acid. The exact mechanism of action of how this inhibition enhances GABA levels in the brain is still the subject of much debate (i.e., from an indirect stimulation of GAD to an inhibition of GABA-T).




Valproic acid (VPA)



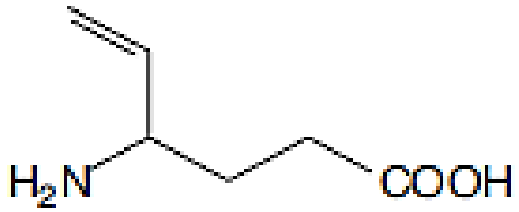

Biosynthesis and metabolism of GABA.

GABA, after its release from the synaptic nerve terminal, is degraded by another pyridoxal dependent enzyme, the GABA transaminase (GABA-T),which transfers an amino group from GABA to ɣ-keto glutarate producing L-glutamic acid and succinic acid semialdehyde (SSA).

SSA is further oxidized by the action of the enzyme succinic semialdehyde dehydrogenase (SSADH, an aldehyde dehydrogenase) to succinic acid that can enter the TCA cycle for the production of additional ɣ-keto glutarate or be further reduced by SSA reductase (an alcohol dehydrogenase that catalyzes the interconversion of SSA and 4-hydroxybutyric acid).

# Drugs that inhibit GABA degradation

Vigabatrin (γ-vinyl-GABA) is an irreversible inhibitor of GABA-T, rationally designed based on the biochemical mechanism of transamination reaction. Briefly, vigabatrin, because of its structural similarity, competes with GABA for binding to GABA-T and forms a Schiff base intermediate with the cofactor, pyridoxal phosphate similar to GABA.



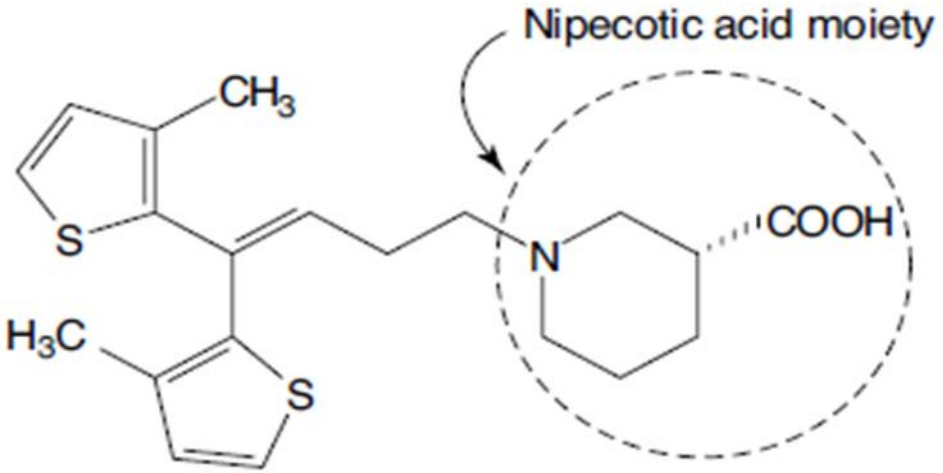

Vigabatrin

However, unlike its substrate GABA, during the process of transferring the amino group to the pyridoxal phosphate, a reactive intermediate is formed with vigabatrin that immediately attaches itself to the active site of the enzyme, thereby irreversibly inhibiting GABA-T and increasing GABA levels in the brain. , It is marketed as an adjunctive treatment of patients with partial seizures.

# Drugs that inhibit reuptake of GABA

**Tigabine:** An uptake inhibitor. it blocks GABA reuptake as a major mode of its anticonvulsant activity. Its use is against partial seizures.

Inhibitors of GABA transporter-1(GAT-1inhibitors) increase extracellular GABA concentration in the hippocampus, striatum, and cortex, thereby prolonging the inhibitory action of GABA released synaptically.

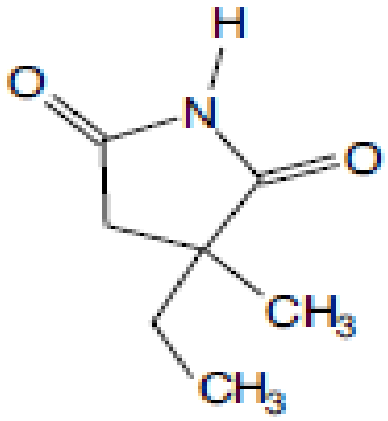



Tiagabine

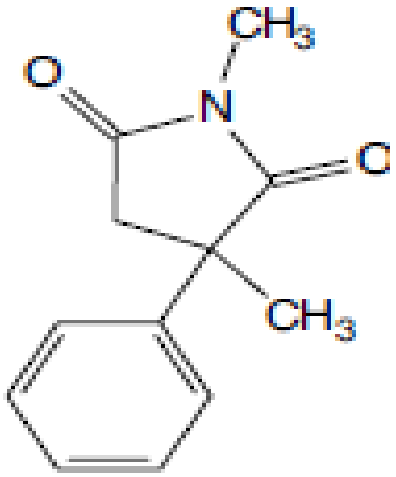
# Ethosuximide (zarontin) and Methsuximide (celontin)

Ethosuximide is considered the prototypical anticonvulsant needed for treating patients with absence seizures.

Ethosuximide and the (N- dealkylated active metabolite) of methsuximide work by blocking the low threshold T-type calcium channels, thereby reducing the hyper excitability of thalamic neurons that is specifically associated with absence seizure.




Ethosuximide

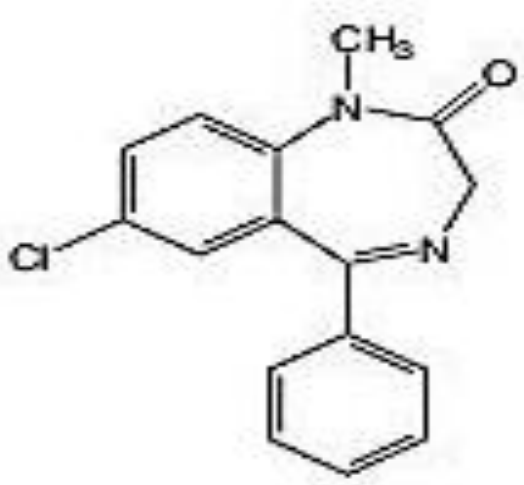



Methsuximide

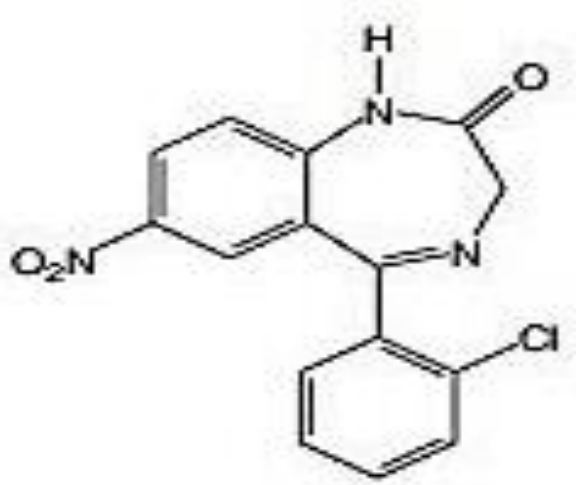
# Benzodiazepines (acts on a selective molecular target)

**Clonazepam:** is useful in absence seizures and in myoclonic seizures. Tolerance to the anticonvulsant effect of the clonazepam often developed rather quickly, and it is a common problem with the BZDs.

**Diazepam:** is given orally (Valium) or rectally (Diastat) as an adjunctive treatment in patients with generalized tonic–clonic status epilepticus.




Diazepam



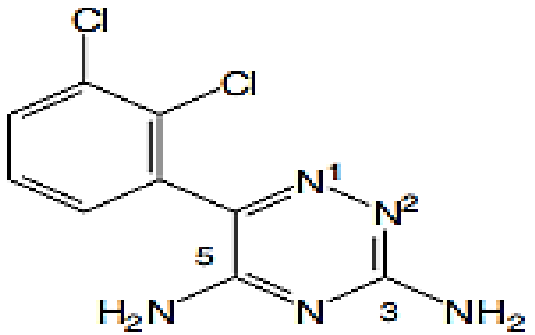

Clonazepam

# Novel Broad-Spectrum Anticonvulsants

Lamotrigine, an AED of the phenyltriazine class, has been found effective against refractory partial seizures.

Like phenytoin and CBZ, its main mechanism of action appears to be:

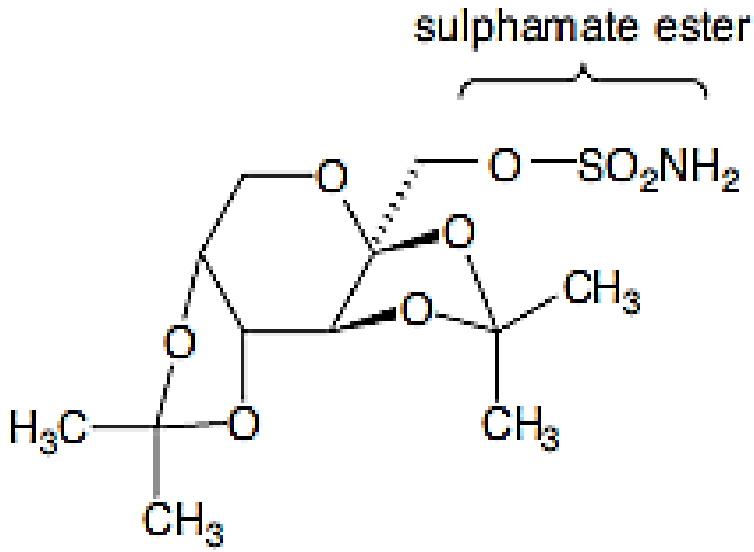
- Blockade of sodium channels that is both voltage- and use dependent.
- inhibits the high-threshold calcium channel, possibly through inhibition of presynaptic N-type calcium channels
- Blocks glutamate release.




Lamotrigine

# Topiramate (topamax)

TPM is a sulphamate-substituted monosaccharide, a derivative of the naturally occurring sugar D-fructose that exhibits broad and potent AED actions at both glutamate and GABA receptors. It has good oral bioavailability of 85% to 95%, most likely resulting from its structural similarity to D-glucose. Thus, it may be actively transported into the brain by the D-glucose transporter.

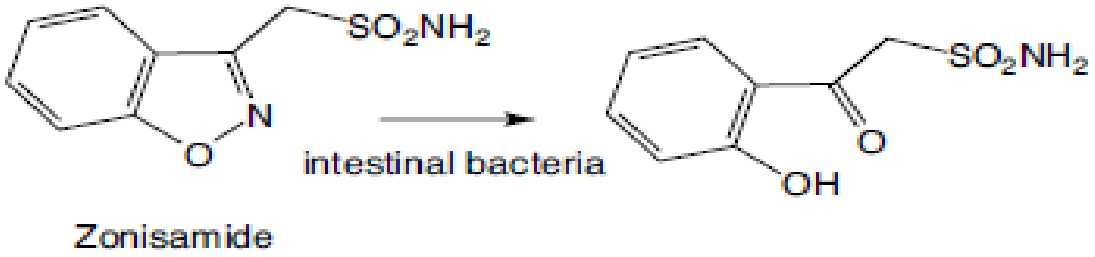



Topiramate

# Zonisamide (zonegran, excegran)

Zonisamide, a sulfonamide-type anticonvulsant was recently approved for adjunctive therapy in the treatment of partial seizures in adults with epilepsy. Zonisamide is primarily metabolized by reductive ring cleavage of the 1,2-benzisoxazole ring to 2-sulfamoyl-acetyl-phenol.

This biotransformation is mainly carried out by the intestinal bacteria rather than the mammalian cytosolic aldehyde oxidase suggested earlier. Again, because of the presence of a sulfonamide moiety in zonisamide molecule, precaution should be given to patients who have a history of hypersensitivity reactions toward sulfonamide drugs and concomitant use of zonisamide with other carbonic anhydrase inhibitors should also be avoided.



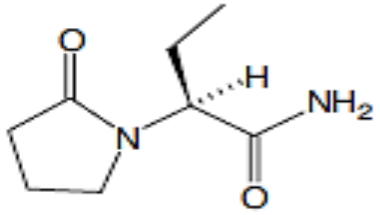

Zonisamide

# Levetiracetam (keppra)

LEV is an analog of the nootropic agent, piracetam.

Only the S-isomer has any anticonvulsant activity. Unlike piracetam, LEV does not have any affinity for the AMPA receptor (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) thereby has no nootropic activity for the treatment of Alzheimer disease. LEV also has no affinity for GABA receptors, BZD receptors, the various excitatory amino acid related receptors, or the voltage-gated ion channels.

For this reason, its mechanism of anticonvulsant action remains unclear, but it appears to exert its antiepileptic action by modulating kainite/AMPA-induced excitatory synaptic currents, thus decreasing membrane conductance.




Levetiracetam


THANK
YOU