DRUGS THAT ACT IN THE CNS

Drugs for Epilepsy 2

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Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

F. Felbamate

Felbamate has a broad spectrum of anticonvulsant action with multiple proposed mechanisms including the blocking of voltage-dependent **sodium channels**, competing with the glycine coagonist binding site on the N-methyl-d-aspartate (**NMDA**) glutamate receptor, blocking of **calcium channels**, and potentiating **GABA** action.

It is an **inhibitor** of drugs metabolized by CYP2C19 and **induces** drugs metabolized by CYP3A4.

It is reserved for use in refractory epilepsies (particularly Lennox-Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

G. Gabapentin

Gabapentin is an **analog of GABA**. However, it **does not** act at GABA receptors, enhance GABA actions or convert to GABA.

Its precise mechanism of action is **not known**. It is approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia.

Gabapentin exhibits **nonlinear pharmacokinetics** due to its uptake by a saturable transport system from the gut.

Gabapentin does not bind to plasma proteins and is excreted unchanged through the kidneys. Reduced dosing is required in renal disease.

H. Lacosamide

Lacosamide affects voltage-gated **sodium channels**, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.

Lacosamide binds to **collapsin response mediator protein-2 (CRMP-2)**, a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth.

The role of CRMP-2 binding in seizure control is unknown.

Lacosamide is approved for **adjunctive treatment of focal seizures**. It is available in an injectable formulation.

The most common adverse events that limit treatment include **dizziness, headache, and fatigue.**

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

I. Lamotrigine

Lamotrigine blocks **sodium channels**, as well as high voltage-dependent **calcium channels**.

Lamotrigine is effective in a wide **variety of seizure types**, including focal, generalized, absence seizures, and Lennox-Gastaut syndrome. It is also used to treat **bipolar disorder**.

As with other antiepilepsy medications, **general inducers** increase lamotrigine clearance leading to lower lamotrigine concentrations, whereas **sodium valproate** results in a significant decrease in lamotrigine clearance (higher lamotrigine concentrations).

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

J. Levetiracetam

Levetiracetam is approved for **adjunct therapy** of focal onset, myoclonic, and primary generalized tonic–clonic seizures in adults and children.

The exact mechanism of anticonvulsant action is unknown. **It demonstrates high affinity for a synaptic vesicle protein (SV2A).**

The drug is well absorbed orally and excreted in urine mostly unchanged, resulting in few to no drug interactions.

Levetiracetam can cause **mood alterations** that may require a dose reduction or a change of medication.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

K. Oxcarbazepine

Oxcarbazepine is a prodrug that is rapidly reduced to the 10-monohydroxy (**MHD**) metabolite responsible for its anticonvulsant activity.

MHD blocks **sodium channels**, preventing the spread of the abnormal discharge. It is also thought to modulate calcium channels.

It is approved for use in adults and children with **partial-onset seizures**.

Oxcarbazepine is a **less potent inducer** of CYP3A4 and UGT than carbamazepine.

The adverse effect of **hyponatremia** limits its use in the elderly.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

L. Perampanel

Perampanel is a selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid **AMPA antagonist** resulting in reduced excitatory activity.

Perampanel has a long half-life enabling once-daily dosing.

It is approved for **adjunctive treatment** of partial-onset seizures in patients 12 years or older.

Perampanel is a **newer antiepileptic** agent, and limited data are available in patients.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

M. Phenobarbital and primidone

The primary mechanism of action of phenobarbital is enhancement of the inhibitory effects of **GABA**-mediated neurons.

Primidone is **metabolized** to phenobarbital (major) and phenylethylmalonamide, both with anticonvulsant activity.

Phenobarbital is used primarily in the treatment of **status epilepticus** when other agents fail.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

N. Phenytoin

Phenytoin blocks voltage-gated **sodium channels** by selectively binding to the channel in the inactive state and slowing its rate of recovery.

It is effective for treatment of focal and generalized **tonic–clonic seizures** and in the treatment of **status epilepticus**.

Phenytoin **induces drugs** metabolized by the CYP2C and CYP3A families.

Phenytoin exhibits **saturable enzyme** metabolism resulting in nonlinear pharmacokinetic properties.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

N. Phenytoin

Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. The elderly are highly susceptible to this effect.

Gingival hyperplasia may cause the gums to grow over the teeth.

Long-term use may lead to development of **peripheral neuropathies and osteoporosis**.

Although phenytoin is advantageous due to its **low cost**, the actual cost of therapy may be much higher, considering the potential for serious **toxicity** and **adverse effects**.

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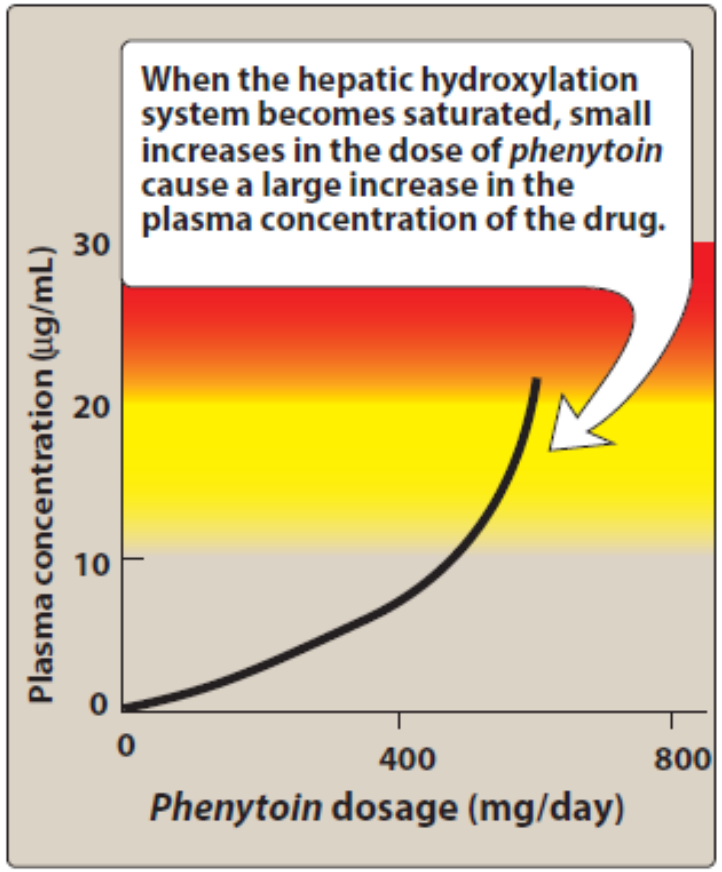
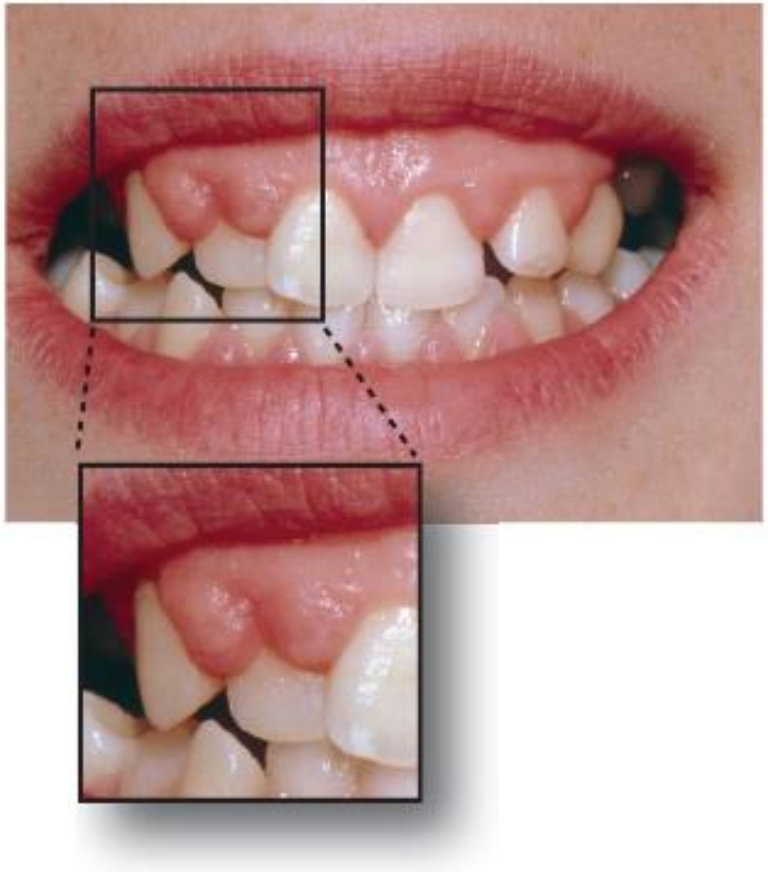
Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

N. Phenytoin



Nonlinear effect of phenytoin dosage on the plasma concentration of the drug.



Gingival hyperplasia in patient treated with phenytoin.

O. Pregabalin

Pregabalin binds to the α2-δ site, an auxiliary subunit of voltage-gated **calcium channels** in the CNS, inhibiting excitatory neurotransmitter release.

The exact role this plays in treatment is not known, but the drug has proven effects on focal-onset **seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia**.

More than 90% of pregabalin is eliminated renally.

It has no significant metabolism and few drug interactions. Weight gain and peripheral edema have been reported.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

P. Rufinamide

Rufinamide acts at **sodium channels**. It is approved for the **adjunctive treatment** of seizures associated with Lennox-Gastaut syndrome in children and in adults.

Rufinamide is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes.

Food increases absorption and peak serum concentrations.

Adverse effects include the potential for **shortened QT intervals**.

Patients with familial short QT syndrome should not be treated with rufinamide.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

Q. Tiagabine

Tiagabine **blocks GABA uptake** into presynaptic neurons permitting more GABA to be available for receptor binding, and therefore, it enhances inhibitory activity.

Tiagabine is effective as **adjunctive treatment** in partial-onset seizures.

Tiagabine should not be used for indications other than epilepsy.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

R. Topiramate

It blocks voltage-dependent **sodium channels**, reduces high-voltage **calcium currents** (L type), is a carbonic anhydrase inhibitor, and may act at glutamate (**NMDA**) sites.

Topiramate is effective for use in partial and primary **generalized epilepsy**. It is also approved for prevention of **migraine**.

It inhibits CYP2C19 and is induced by phenytoin and carbamazepine.

Adverse effects include weight loss, and paresthesias. Renal stones, glaucoma, oligohidrosis (decreased sweating), and hyperthermia have also been reported.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

S. Valproic acid and divalproex

Possible mechanisms of action include **sodium channel** blockade, blockade of **GABA** transaminase, and action at the T-type **calcium channels**.

It is effective for the treatment of focal and primary **generalized epilepsies**.

Divalproex sodium is a combination of sodium valproate and valproic acid that is converted to valproate when it reaches the gastrointestinal tract. It was developed to **improve gastrointestinal tolerance of valproic acid**.

Valproate inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems.

Rare **hepatotoxicity** may cause a rise in liver enzymes, which should be monitored frequently. **Teratogenicity** is also of great concern.

T. Vigabatrin

Vigabatrin acts as an irreversible inhibitor of γ-aminobutyric acid transaminase (**GABA-T**). GABA-T is the enzyme responsible for metabolism of GABA.

Vigabatrin is associated with **visual field loss** ranging from mild to severe in 30% or more of patients.

U. Zonisamide

Zonisamide is a **sulfonamide** derivative that has a broad spectrum of action.

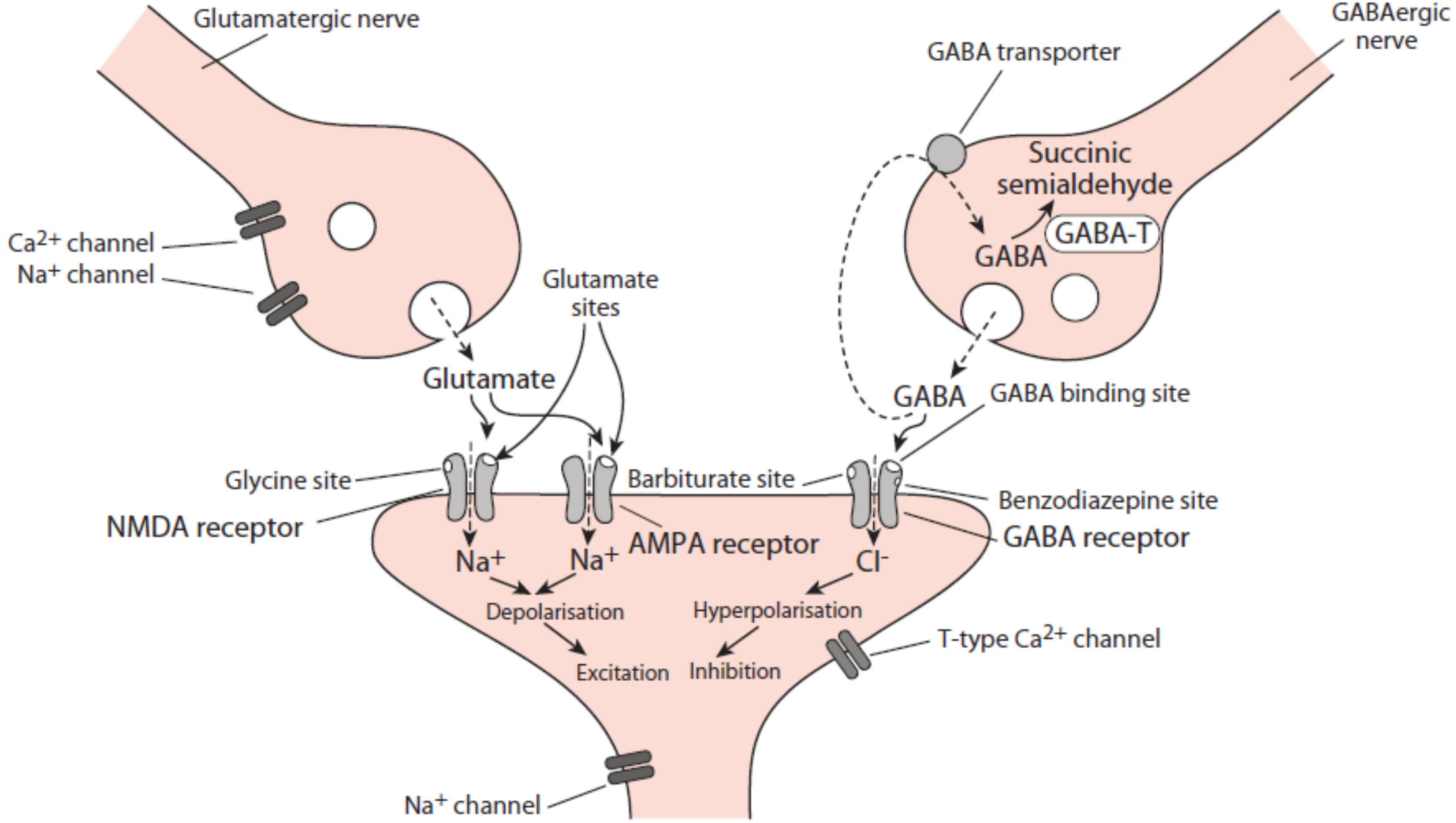
The compound has multiple effects, including blockade of both voltage-gated **sodium** channels and T-type **calcium** currents.

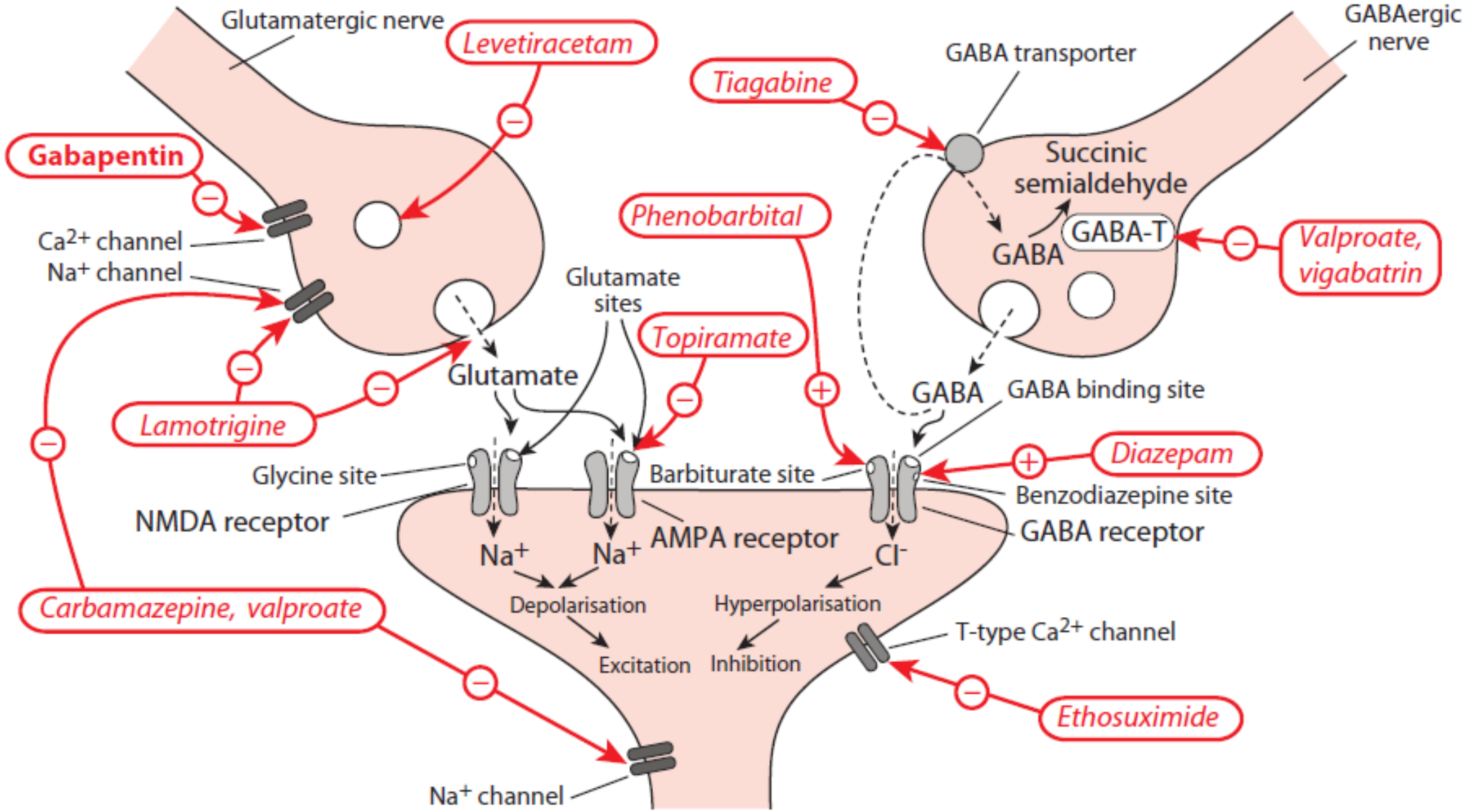
Zonisamide is approved for use in patients with **focal epilepsy**.

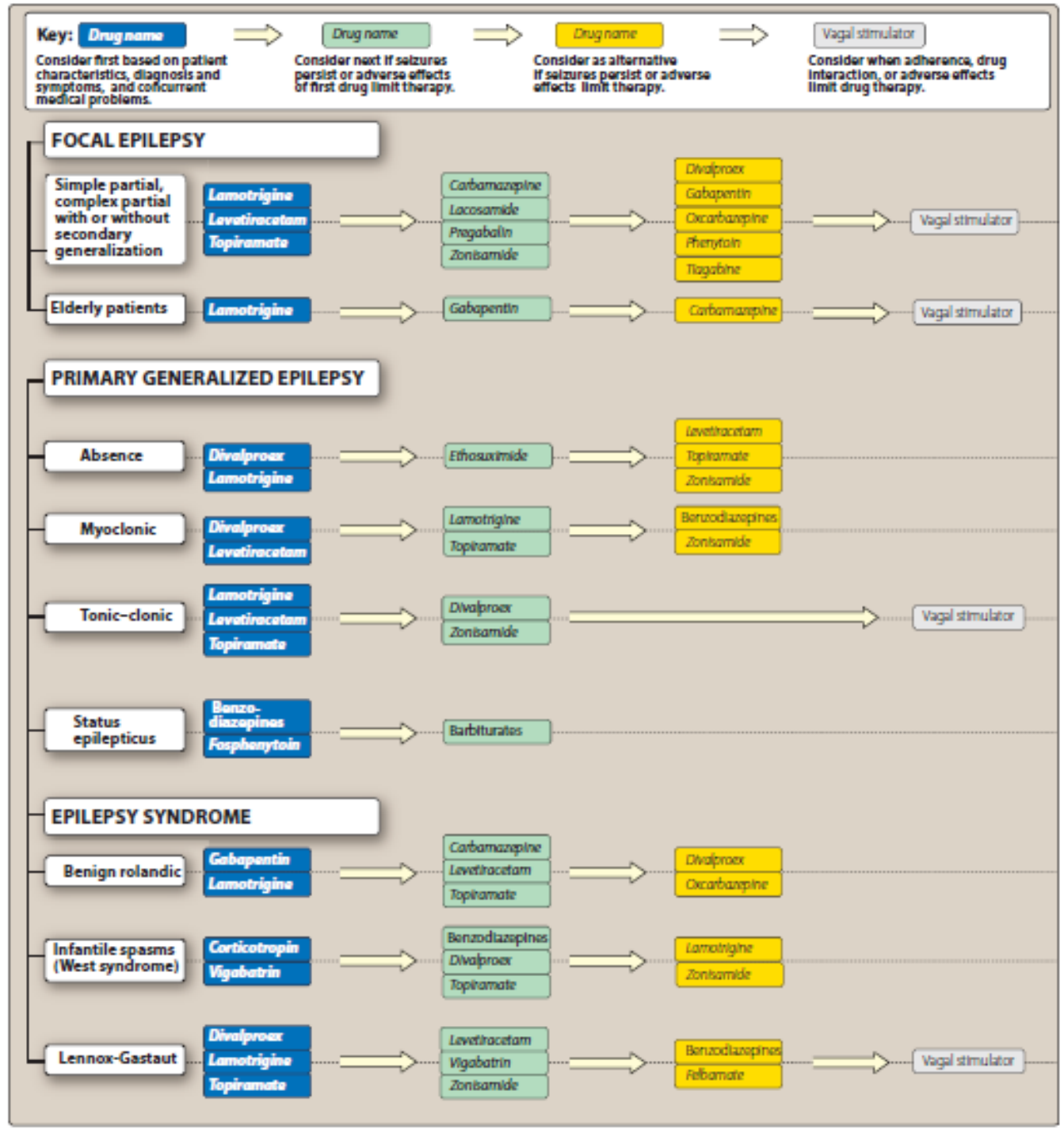
In addition to typical **CNS adverse effects**, zonisamide may cause **kidney** stones. **Oligohidrosis** has been reported, and patients should be monitored for increased body temperature and decreased sweating.

Zonisamide is contraindicated in patients with sulfonamide or carbonic anhydrase inhibitor **hypersensitivity**.

Potential sites of action of antiepileptic drugs




Glutamatergic nerve
Levetiracetam
Gabapentin
Ca2+ channel
Na+ channel
Lamotrigine
Glutamate
Glutamate sites
Topiramate
Phenobarbital
Tiagabine
GABA transporter
GABAergic nerve
Succinic semialdehyde
GABA
GABA-T
Valproate, vigabatrin
GABA
GABA binding site
Diazepam
Benzodiazepine site
GABA receptor
Glycine site
NMDA receptor
Barbiturate site
AMPA receptor
Na+
Na+
Cl-
Depolarisation
Hyperpolarisation
Excitation
Inhibition
Carbamazepine, valproate
T-type Ca2+ channel
Ethosuximide
Na+ channel


Key:
Drug name
Consider first based on patient characteristics, diagnosis and symptoms, and concurrent medical problems.
Drug name
Consider next if seizures persist or adverse effects of first drug limit therapy.
Drug name
Consider as alternative if seizures persist or adverse effects limit therapy.
Vagal stimulator
Consider when adherence, drug interaction, or adverse effects limit drug therapy.
FOCAL EPILEPSY
Simple partial, complex partial with or without secondary generalization
Lamotrigine
Levetiracetam
Topiramate
Carbamazepine
Lacosamide
Pregabalin
Zonisamide
Divalproex
Gabapentin
Oxcarbazepine
Phenytoin
Tiagabine
Vagal stimulator
Elderly patients
Lamotrigine
Gabapentin
Carbamazepine
Vagal stimulator
PRIMARY GENERALIZED EPILEPSY
Absence
Divalproex
Lamotrigine
Ethosuximide
Levetiracetam
Topiramate
Zonisamide
Myoclonic
Divalproex
Levetiracetam
Lamotrigine
Topiramate
Benzodiazepines
Zonisamide
Tonic–clonic
Lamotrigine
Levetiracetam
Topiramate
Divalproex
Zonisamide
Vagal stimulator
Status epilepticus
Benzo-diazepines
Fosphenytoin
Barbiturates
EPILEPSY SYNDROME
Benign rolandic
Gabapentin
Lamotrigine
Carbamazepine
Levetiracetam
Topiramate
Divalproex
Oxcarbazepine
Infantile spasms (West syndrome)
Corticotropin
Vigabatrin
Benzodiazepines
Divalproex
Topiramate
Lamotrigine
Zonisamide
Lennox-Gastaut
Divalproex
Lamotrigine
Topiramate
Levetiracetam
Vigabatrin
Zonisamide
Benzodiazepines
Felbamate
Vagal stimulator

ANTIEPILEPSY MEDICATION	PROTEIN BINDING*	HALF-LIFE	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION	DRUG INTERACTIONS
Carbamazepine	Moderate	6–15	CBZ-10,11-epoxide	Liver	✔
Eslicarbazepine acetate **^	Low	8–24	Eslicarbazepine (S-licarbazepine)	Kidney	✔
Ethosuximide	Low	25–26		Liver	✔
Ezogabine	Moderate	7–11	monoacetylated metabolite	Liver	✔
Felbamate	Low	20–23		Kidney/Liver	✔
*Fosphenytoin***	High	12–60	phenytoin	Liver	✔
Gabapentin	Low	5–9		Kidney	
Lacosamide	Low	13		Various	
Lamotrigine	Low	25–32		Liver	✔
Levetiracetam	Low	6–8		Hydrolysis	
*Oxcarbazepine***	Low	5–13	Monohydroxy metabolite (MHD)	Liver	✔
Phenobarbital	Low	72–124		Liver	✔
Phenytoin	High	12–60		Liver	✔
Primidone	High	72–124	Phenobarbital, PEMA	Liver	✔
Perampanel^	High	105		Liver	✔
Pregabalin	Low	5–6.5		Kidney	
Rufinamide	Low	6–10		Liver	✔
Tiagabine	High	7–9		Liver	✔
Topiramate	Low	21		Various	✔
Vigabatrin	Low	7.5		Kidney	✔
Valproic Acid (Divalproex)	Moderate/ High	6–18	Various	Liver	✔
Zonisamide	Low	63		Liver	✔