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EPILEPSY

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DISCLOSURE

None

OBJECTIVES

1. Identify the appropriate medications for managing tonic-clonic/focal, absence, and myoclonic seizures
2. Identify the appropriate medications for managing status epilepticus
3. Explain mechanisms of action for medications used to manage epilepsy and correlate with underlying pathophysiology
4. Describe adverse effects and contraindications to medications for managing epilepsy, including those that inhibit excitation (inhibitors of glutamate release [sodium channel blockers and others]) and enhance inhibition (T type calcium channel blockers, enhancers of gamma-aminobutyric acid).
5. Describe the clinically important drug interactions of medications used to manage epilepsy, including those that including those that inhibit excitation (inhibitors of glutamate release [sodium channel blockers and others]) and enhance inhibition (T type calcium channel blockers, enhancers of gamma-aminobutyric acid).

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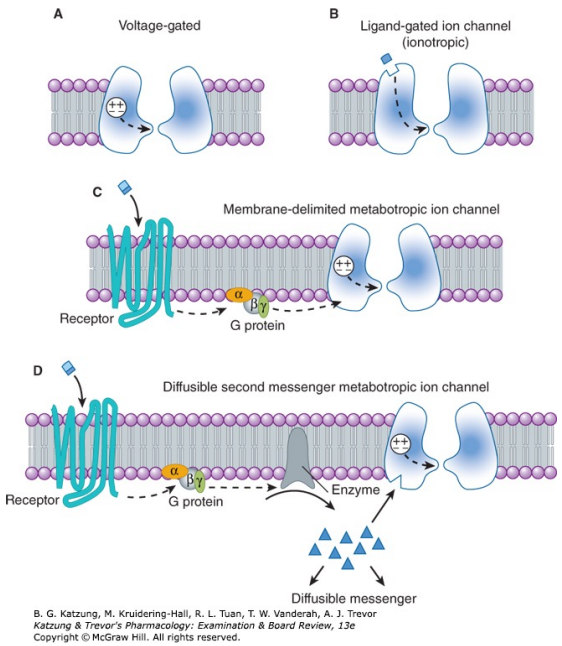
INTRO TO NEUROPHARMACOLOGY

TARGETS OF CNS DRUG ACTION

Most CNS drugs act by

1. Changing ion flow through transmembrane channels of nerve cells
2. Altering transmitter reuptake transporters
3. Inhibiting of neurotransmitter metabolism (such as acetylcholine and GABA)
4. Altering function of neuroglia

ION CHANNELS



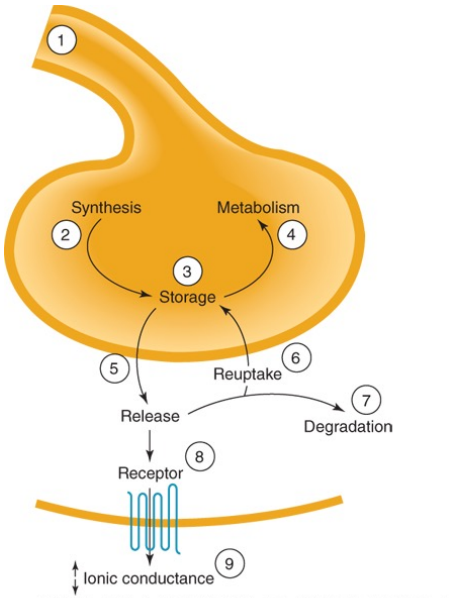
Excitatory (depolarizing) postsynaptic potentials (EPSPs) are usually generated by the opening of sodium or calcium channels

- In some synapses, similar depolarizing potentials result from the closing of potassium channels

Inhibitory (hyperpolarizing) postsynaptic potentials (IPSPs) are usually generated by the opening of potassium or chloride channels

- Activation of postsynaptic metabotropic receptors increases the efflux of potassium
- Presynaptic inhibition can occur via a decrease in calcium influx elicited by activation of metabotropic receptors

SITES OF CNS DRUG ACTION



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

1. The action potential in the presynaptic fiber
2. Synthesis of transmitter
3. Storage
4. Metabolism
5. Release
6. Reuptake
7. Degradation
8. Receptor for the transmitter
9. Receptor-induced decrease or increase in ionic conduction

TRANSMITTERS AT CENTRAL SYNAPSES

Neurotransmitters must

1. Be present in higher concentration in the synaptic area than in other areas (ie, must be localized in appropriate areas)
2. Be released by electrical or chemical stimulation via a calcium-dependent mechanism
3. Produce the same sort of postsynaptic response that is seen with physiologic activation of the synapse (ie, must exhibit synaptic mimicry)

MAJOR NEUROTRANSMITTERS IN THE CNS

Glutamate
- Most important **EXCITATORY** transmitter in the CNS

GABA
- Most important **INHIBITORY** transmitter in the CNS

Acetylcholine

Dopamine

Norepinephrine

Serotonin

Peptide transmitters

Endocannabinoids

GLUTAMATE

Most important EXCITATORY transmitter in the CNS

- Most neurons in brain EXCITED by glutamic acid

Receptor Type	Receptor Mechanism	Relevant Drugs
N-methyl-D-aspartate (NMDA) receptor	Excitatory; ↑ Ca^{2+} or cation conductance	Blocked by phencyclidine, ketamine, memantine (Alzheimer's disease)
AMPA	Excitatory; ↑ Na+, K+ current	Blocked by perampanel (epilepsy)
Kainate	Excitatory; ↑ Na+, K+ current	Inactivated by marine toxin domoic acid

GABA

Most important INHIBITORY transmitter in the CNS

GABA Receptor	Receptor Mechanism	Relevant Drugs
GABA-A	Inhibitory; ↑ Cl^- conductance	Sedative hypnotics (barbiturates, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists) Selected anticonvulsants (gabapentin, tiagabine, vigabatrin)
GABA-B	Inhibitory (presynaptic); ↓ Ca2+ conductance Inhibitory (postsynaptic); ↑ K+ conductance	Agonists (baclofen)

ACETYLCHOLINE

~5% brain neurons have receptors for acetylcholine (ACh)

Acetylcholinesterase inhibitors used in Alzheimer's disease (rivastigmine)

Receptor Type	Receptor Mechanisms	Relevant Drugs
M1	Excitatory; ↓ K+ conductance; ↑ IP3 and DAG	Blocked by pirenzepine and atropine Muscarinic blocking inhibitors used in parkinsonism (benztropine)
M2	Inhibitory; ↑ K+ conductance; cAMP	Blocked by atropine
Nicotinic	Excitatory; ↑ cation conductance	Nicotine

DOPAMINE

Exerts slow inhibitory actions in specific neuronal systems

Receptor Type	Receptor Mechanisms	Relevant Drugs
D1	Stimulatory; ↑ cAMP	Blocked by phenothiazines
D2	Inhibitory (presynaptic); ↓ Ca2+ conductance Inhibitory (postsynaptic); ↑ K+ conductance; ↓ cAMP	Blocked by phenothiazines and haloperidol

NOREPINEPHRINE

Noradrenergic neuron cell bodies mainly located in brain stem and lateral tegmental area of pons

Involved in mood, appetite, alertness

- Excitatory: Alpha-1 and beta-1; Inhibitory: Alpha-2 and beta-2

Receptor Types	Receptor Mechanisms	Relevant Drugs
Alpha-1	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG	Blocked by prazosin
Alpha-2	Inhibitory (presynaptic); ↓ Ca^{2+} conductance	Activated by clonidine
Beta-1	Excitatory; ↓ K^+ conductance; ↑ cAMP	Blocked by propranolol
Beta-2	Inhibitory; ↑ electrogenic sodium pump	Blocked by propranolol

SEROTONIN

Cell bodies in midbrain and pons project to all levels

- 5-HT1A and GABA-B receptors share same K+ channel
- Cause excitation or inhibition depending on subtype

Receptor Types	Receptor Mechanisms	Relevant Drugs
5-HT1A	Inhibitory; ↑ K+ conductance	Buspirone is a partial agonist
5-HT2A	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG	Blocked by clozapine, risperidone, and olanzapine
5-HT3	Excitatory; ↑ cation conductance	Blocked by ondansetron
5-HT4	Excitatory; ↓ K^+ conductance; ↑ cAMP	

ACTIVE LEARNING

What is the most important excitatory neurotransmitter in the CNS?

What is the most important inhibitory neurotransmitter in the CNS?

With this is mind, how might you modulate each neurotransmitter in the treatment of epilepsy?

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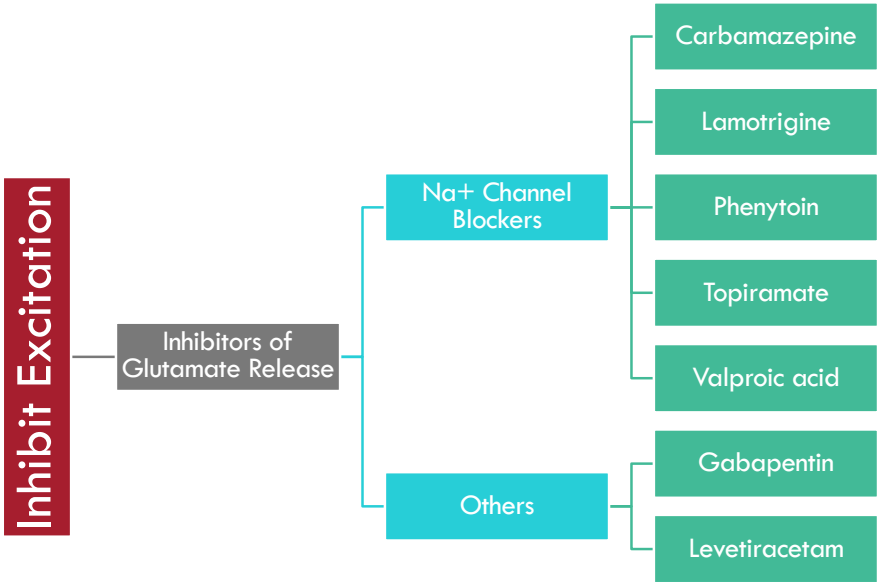
DRUGS FOR EPILEPSY

Pharmacology

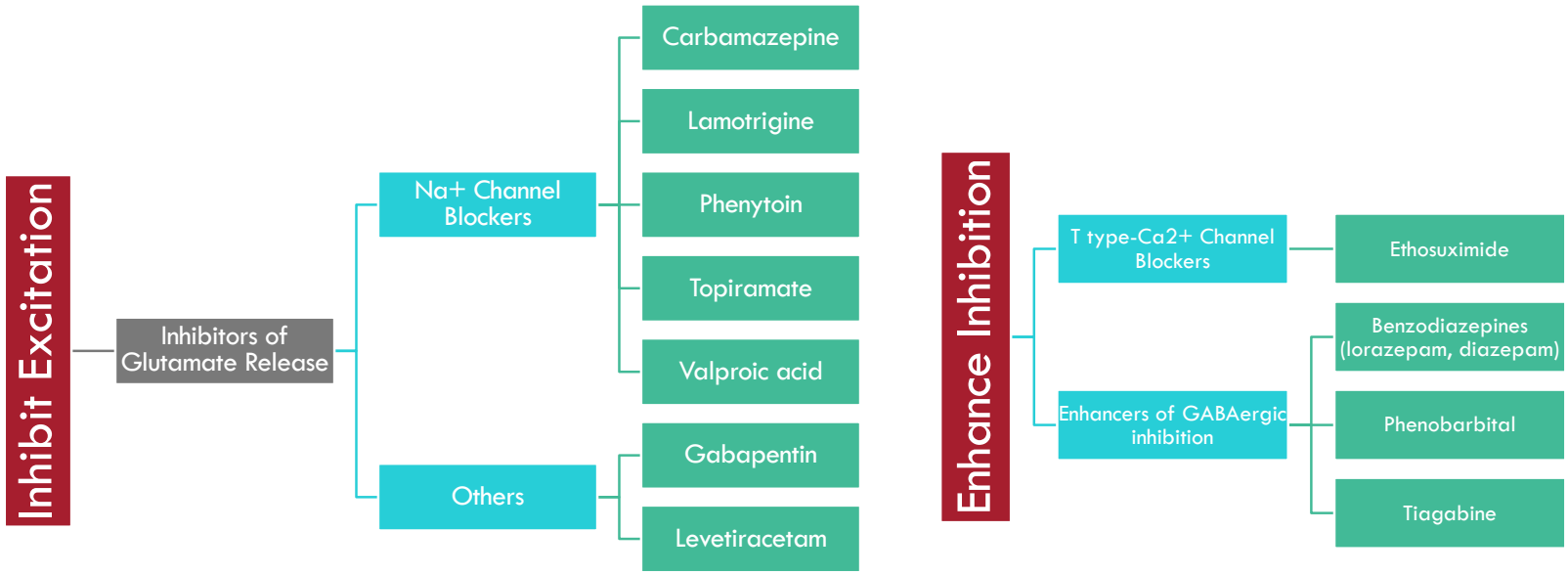
PHARM STRATEGIES FOR SEIZURES

1. Inhibit glutamate
2. Enhance GABA
3. Prevent neuronal depolarization (by stabilizing resting membrane action potential) and degranulation
4. Other

DRUGS FOR SEIZURES



DRUGS FOR SEIZURES



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INHIBITORS OF GLUTAMATE RELEASE

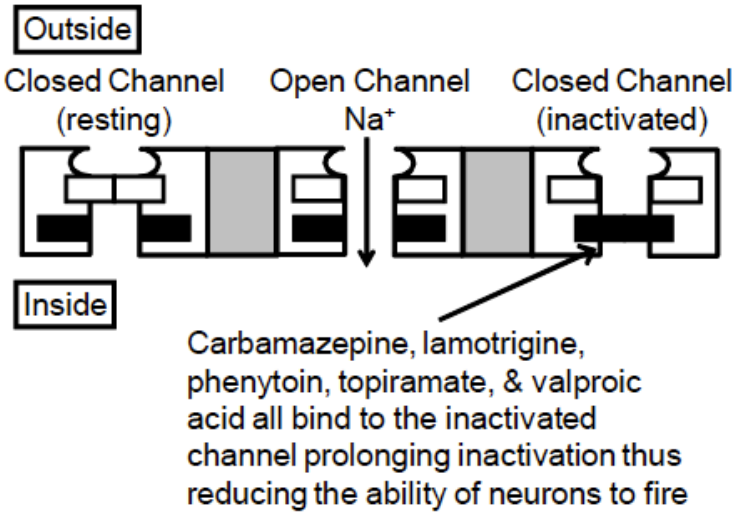
NA+ CHANNEL BLOCKER MECHANISM OF ACTION

At resting potential

- Most m-gates (open boxes) are closed
- H-gates (solid-boxes) are open (Closed Channel-resting)

Depolarization causes m-gates to open (Open Channel) and Na+ enters the cell causing an action potential and intense depolarization which causes the h-gates to close the channel (Closed Channel-inactivated)

The Na+ channel blockers preferentially bind to the inactivated sodium channel (similar to local anesthetics)



CARBAMAZEPINE

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Carbamazepine (Tegretol)	Hypersensitivity to TCAs **MAOI use w/in 14 days** **HLA-B*1502 allele** Bone marrow depression Hepatic porphyria Abrupt discontinuation Cautions: Pregnancy, Asian patients (increased HLA-B*1502 prevalence), hepatic impairment, absence seizures	Drowsiness Cerebellovestibular changes (ataxia, vertigo, and diplopia) Skin rashes (Stevens-Johnson Syndrome) Blood dyscrasias (agranulocytosis, aplastic anemia) Teratogenicity (cleft lip/palate, spina bifida) SIADH	**Drug can induce its own metabolism (autoinduction) - may need to readjust dose after measuring blood levels** Can induce metabolism of other antiseizure drugs and other drugs metabolized in the liver Other drugs which can induce or inhibit (eg, cimetidine, macrolide antibiotics) P450 enzymes can affect carbamazepine blood levels accordingly

CARBAMAZEPINE ADME

Metabolized in the liver; metabolite is pharmacologically active

Induces liver enzymes (important drug interactions)

Narrow therapeutic window

THERAPEUTIC INDEX

Measure of drug safety

- Drug with a higher therapeutic index is safer than one with a low therapeutic index
- Can use lethal dose or toxic dose
  - The toxic dose is the dose that is toxic to 50% of those that receive it
  - The lethal dose is the dose that is lethal to 50% of those that receive it

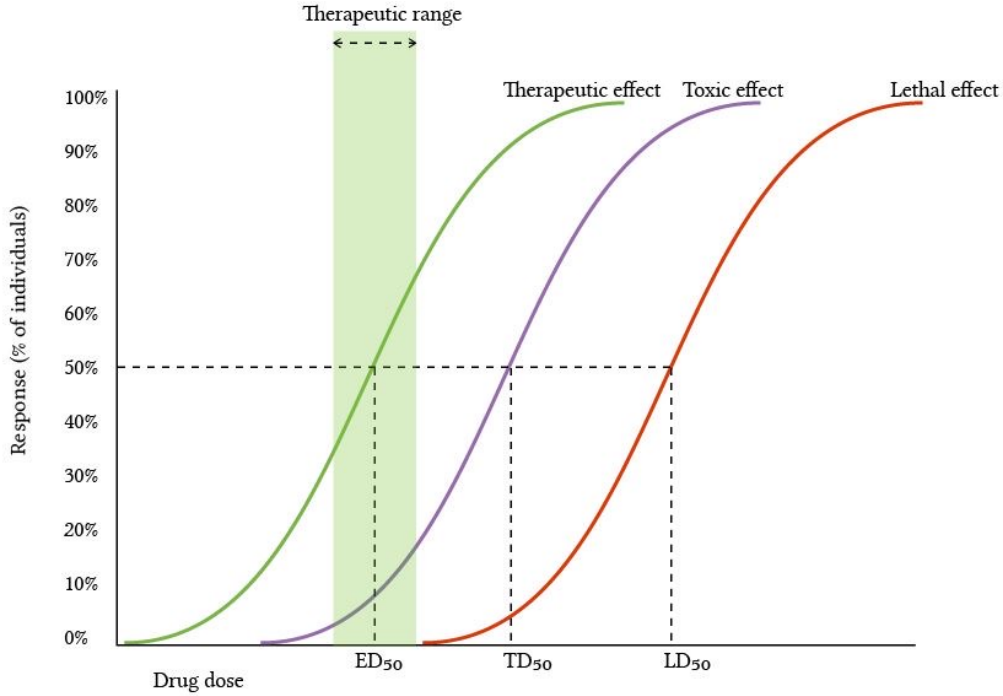
$$Therapeutic\ Index = \frac{median\ toxic\ dose}{median\ effective\ dose} = \frac{TD_{50}}{ED_{50}}$$

THERAPEUTIC INDEX

$$Therapeutic\ Index\ =$$

$$\frac{median\ toxic\ dose}{median\ effective\ dose}$$

$$= \frac{TD_{50}}{ED_{50}}$$



CARBAMAZEPINE THERAPEUTIC INDEX

Carbamazepine has a LOW therapeutic index

- There is little difference between the median toxic dose and the median effective dose
- Therapeutic range 4 – 12 mcg/mL

$$Therapeutic\ Index\ = \frac{median\ toxic\ dose}{median\ effective\ dose} = \frac{TD_{50}}{ED_{50}}$$

ACTIVE LEARNING

A pharmacodynamic study in five patients found carbamazepine to have a median concentration of 6 mcg/mL, but caused toxicity at a median concentration of 18 mcg/mL. What is the therapeutic index of carbamazepine in this study?

LAMOTRIGINE

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Lamotrigine (Lamictal)	Abrupt withdrawal Cautions: pregnancy, renal impairment	Cerebellovestibular changes (ataxia, vertigo, diplopia) **Skin rashes (Stevens-Johnson Syndrome)** **Hemophagocytic lymphohistiocytosis** **CNS depression**	Caution advised with other sodium channel blockers

LAMOTRIGINE ADME

Metabolized in the liver; glucuronidation

PHENYTOIN

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Phenytoin (Dilantin) Fosphenytoin	Abrupt withdrawal Cautions: pregnancy, HLA-B1502 allele, renal impairment, hepatic impairment	**Nystagmus** Cerebellovestibular changes (ataxia, vertigo, diplopia) Skin rashes (Stevens-Johnson Syndrome) **Gingival hyperplasia (up to 50% of patients)** Teratogenic–fetal hydantoin syndrome (cleft lip, cleft palate, congenital heart disease, slowed growth and mental deficiency) Pseudolymphoma Yellow-brown skin Urine discoloration	Inducer of CYP450

PHENYTOIN ADME

Highly bound to plasma proteins (about 90%)

- Can displace, and be displaced by, other drugs
- Valproic acid can displace phenytoin from plasma protein sites increasing its blood levels; may need to decrease phenytoin dose if given with valproic acid.

Displays **zero-order kinetics**

Phenytoin is one of a very few drugs that exhibits zero-order kinetics

Metabolizing enzymes saturated at blood levels needed to control seizures, any increase in dose of phenytoin could cause a disproportionate increase in the drug's concentration in the blood and lead to toxicity

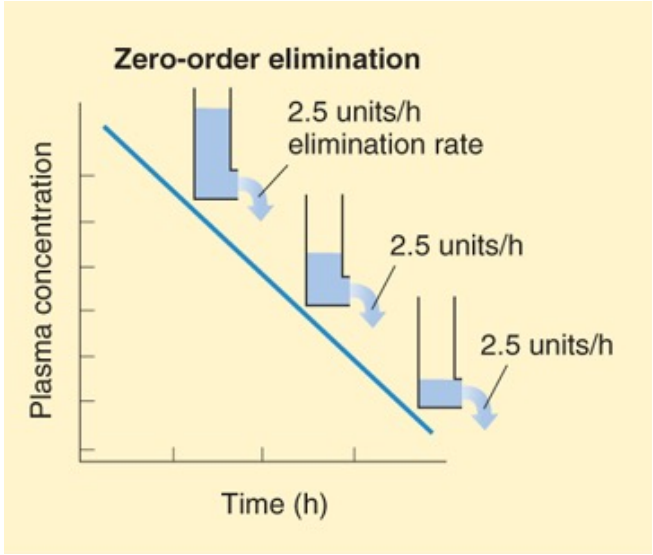
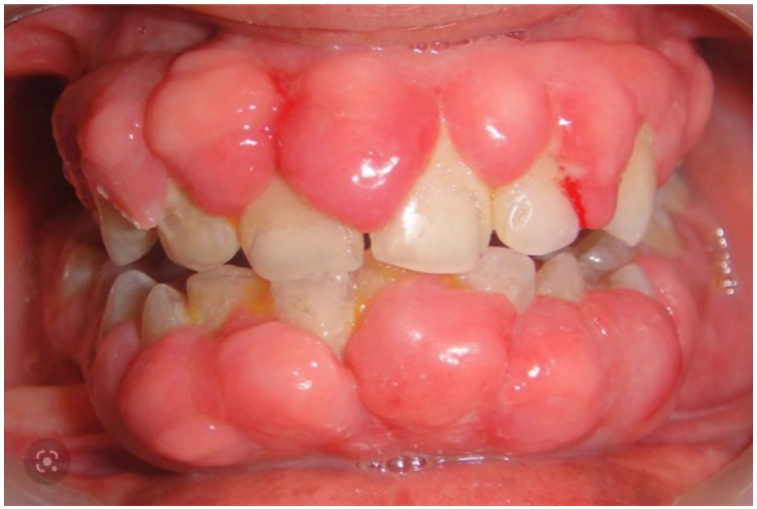


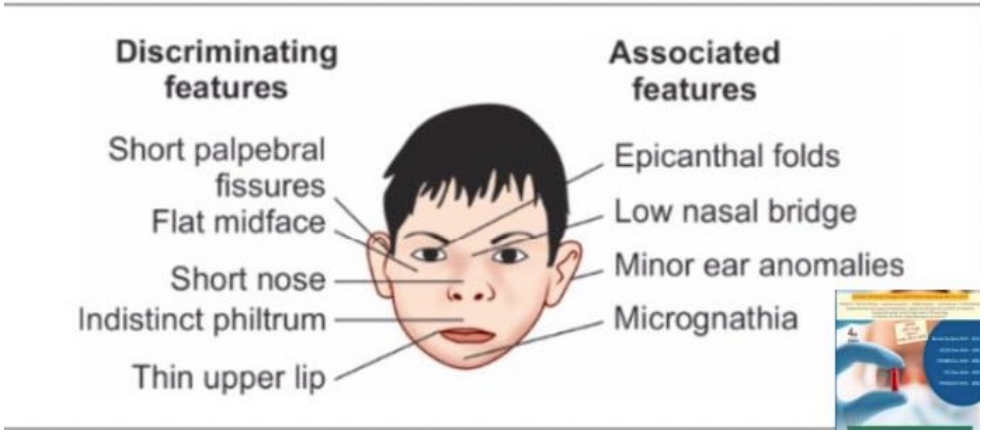
Image from Katzung & Trevor's Pharmacology: Examination & Board Review, 13e; 2021.

PHENYTOIN ADVERSE EFFECTS

Phenytoin-Induced Gingival Hyperplasia



Fetal Hydantoin Syndrome



TOPIRAMATE

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Topiramate (Topamax)	Abrupt withdrawal Cautions: alcohol use	Sedation Slow cognition Kidney stones Weight loss Glaucoma Speech difficulties	Minimal

TOPIRAMATE ADME

Mainly excreted unchanged in the urine

VALPROIC ACID

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Valproic acid (Depakote)	Hepatic dysfunction (may cause fatal hepatotoxicity) Cautions: alcohol use	**Nystagmus** Cerebellovestibular changes (ataxia, vertigo, diplopia) Skin rashes (Stevens-Johnson Syndrome) Hepatotoxicity Teratogen (neural tube defects in first trimester) Alopecia GI effects **Metabolic effects (weight gain)**	Increased CNS depression when used in combination with other CNS depressants Inhibiting P450 inhibits metabolism of other drugs metabolized by P450 enzymes

VALPROIC ACID ADME

Highly bound to plasma proteins (about 90%); can displace phenytoin

Metabolized by liver enzymes

- **Inhibits P450**

Also works as a T-type Ca2+ channel blocker

Also works by enhancing GABAergic inhibition

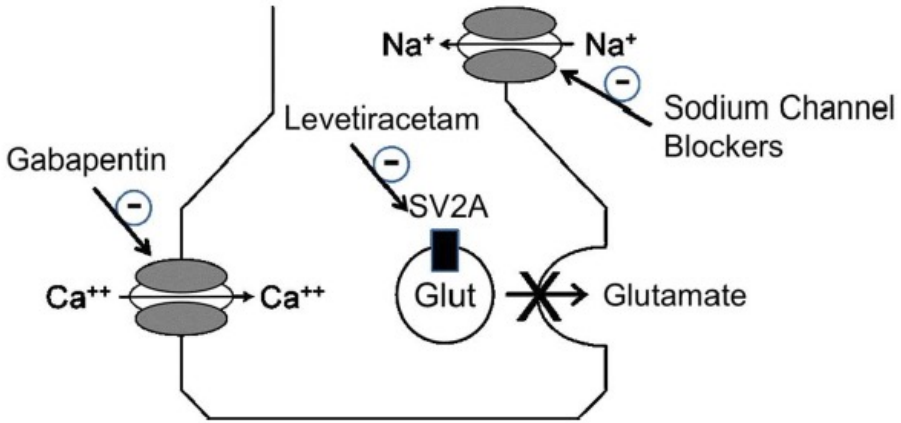
OTHER DRUGS THAT INHIBIT GLUTAMATE RELEASE

Levetiracetam binds selectively to SV2A, a synaptic vesicle integral membrane protein, which may function as a positive effector of synaptic vesicle exocytosis

- Binding to SV2A in the vesicle reduces the release of the excitatory neurotransmitter glutamate

Gabapentin's mechanism is not entirely understood

- Binds to protein subunit of voltage-gated calcium channels which may decrease glutamate release at excitatory synapses



LEVETIRACETAM & GABAPENTIN

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Levetiracetam (Keppra)	Abrupt discontinuation Cautions: Pregnancy	Somnolence Asthenia Ataxia Dizziness Uncommon severe mood changes	None
Gabapentin (Neurontin)	Abrupt discontinuation Cautions: Avoid alcohol	Drowsiness Dizziness	Minimal

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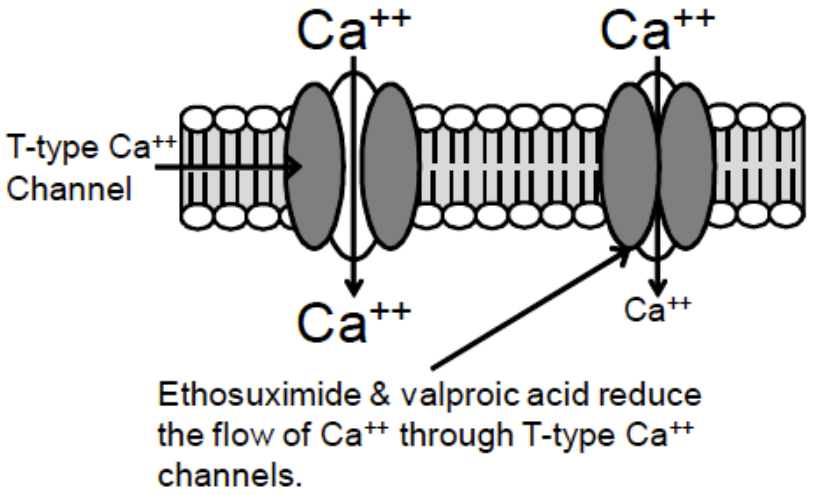
T-TYPE CA2+ CHANNEL BLOCKERS

T-TYPE CA2+ CHANNEL BLOCKER MECHAN. OF ACTION

Reducing the flow of Ca++ through T-type calcium channels reduces the pacemaker current responsible for the thalamic rhythm seen in generalized absence seizures



ETHOSUXIMIDE

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Ethosuximide	Abrupt withdrawal Bone marrow depression	**Blood dyscrasias** (agranulocytosis, pancytopenia, leukopenia) Immune thrombocytopenia Aggressive behavior Fatigue GI disturbances Headache Urticaria **Skin rash (DRESS, Stevens-Johnson syndrome)**	Minimal

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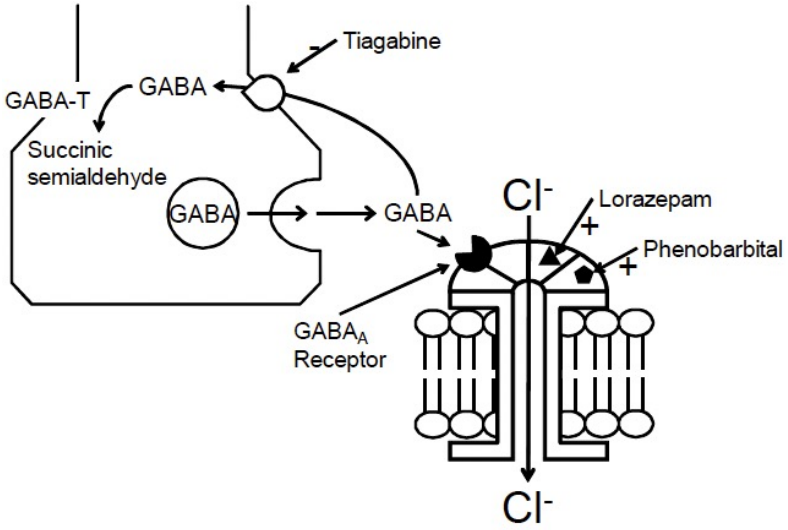
ENHANCERS OF GABAERGIC INHIBITION

ENHANCERS OF GABAERGIC INHIBITION

In the presence of GABA, the GABA-A receptor is opened allowing an influx of Cl-, which in turn increases membrane polarization (hyperpolarization)

ENHANCERS OF GABAERGIC INHIBITION



Tiagabine blocks the active reuptake of GABA into the nerve ending thus increasing the concentration of GABA in the synaptic cleft

Phenobarbital and **benzodiazepines** bind to sites on the GABA-A receptor enhancing the influx of Cl- in response to GABA (similar to general anesthetics)

- The drugs bind to sites on the receptor other than that of GABA potentiating the inhibition (positive allosteric modulators)

Valproic acid also enhances GABAergic inhibition but the mechanism is not clearly understood

ENHANCERS OF GABAERGIC INHIBITION

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Benzodiazepines (lorazepam, diazepam) *Reversal agent is flumazenil*	Abrupt withdrawal Glaucoma Caution: Alcohol use	Sedation Tolerance Potential dependence Respiratory depression	Additive CNS depression Hepatic metabolism Active metabolites (diazepam)
Phenobarbital	Abrupt withdrawal Hepatic impairment Caution: Females of reproductive potential	Sedation Tolerance Potential dependence Respiratory depression Ataxia	Inducer of CYP Many interactions
Tiagabine	Abrupt withdrawal Caution: Alcohol use	Dizziness Nervousness Depression Seizures	CYP3A4 substrate

ACTIVE LEARNING

A 24-year-old man was found unresponsive with an empty bottle of phenobarbital pills next to him. He was rushed to the ED. Which statement concerning management of this patient is most accurate?

A. Acidification of the urine accelerates the elimination of phenobarbital

B. Alkalinization of the urine accelerates the elimination of phenobarbital

C. Flumazenil will reverse the effects of phenobarbital

D. Compared with phenobarbital, the benzodiazepines exhibit a steeper dose-response relationship

E. Respiratory depression caused by barbiturate overdosage can be reversed by flumazenil

WEAK ACIDS

$$HA \leftrightarrows H^+ + A^-$$

pK is the equilibrium constant

- pH = pK, there are equal amounts of weak acid in the ionized and nonionized forms
- pH < pK (add more H^+), drive the equilibrium to the left and there is more protonated (nonionized) form
- pH > pK (take away H^+), drive the equilibrium to the right and there is more unprotonated (ionized) form

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CLINICAL USE

SUMMARY OF INDICATIONS/CLINICAL USE

Drug	Seizure Disorder				
	Focal Seizures	Generalized Seizures			Status Epilepticus
		Tonic-clonic	Myoclonic	Absence	
Carbamazepine	1				
Lamotrigine	1	1	1*	A	
Levetiracetam	1	1	1	A	
Valproic acid	A	1	1	1	
Ethosuximide				1	
Topiramate	A	A	A		
Lorazapam					1
Gabapentin	A				
Phenobarbital	A	A			
Phenytoin	A				
Tiagabine	A				

1=First-line drug; A=Alternative
*lamotrigine may worsen myoclonus other than juvenile myoclonic epilepsy where lamotrigine is a first-choice medication

STATUS EPILEPTICUS

Prolonged seizures which continue or occur in rapid succession with relatively brief intervals in between

Benzodiazepines first choice

- Given every 5 – 10 minutes until seizures terminate
- Seizures may reoccur unless a longer acting anticonvulsant administered or subtherapeutic anticonvulsant level brought back into therapeutic range

PREGNANCY

Most pregnant patients exposed to antiepileptic drugs deliver normal infants, but fetal exposure to older anticonvulsants has been associated with congenital anomalies, including oral cleft and cardiac, urinary tract and neural tube defects

- Carbamazepine, valproate, phenobarbital, and phenytoin associated with teratogenic effects
- Clinical data regarding the teratogenicity of other newer antiepileptic drugs is less clear

All agents should be used in monotherapy at the lowest dose possible; the risk to offspring is considered to be less than the risk of seizures during pregnancy

PREGNANCY

Prophylactic folic acid use recommended for all women of childbearing age because it has decreased the incidence of neural tube defects

- May not be protective in women who take antiepileptic drugs during pregnancy

Phenytoin, phenobarbital, and carbamazepine may cause hemorrhage in the newborn infant due to vitamin K deficiency

- Vitamin K supplementation recommended for mother in the final month of pregnancy and for the newborn

GUIDING YOUR STUDY PRIORITIES

Mechanism of action

Unique adverse effects

Drug classes for seizure types that have few treatments (absence seizures, status epilepticus)

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ANY QUESTIONS?