PHARMACOLOGY

Drugs for Seizures

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DISCLOSURE

None

Use Statement

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.
5. Describe the clinically important drug interactions of medications used to manage epilepsy.

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INTRO TO NEUROPHARMACOLOGY

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?

ACTIVE LEARNING

What is the most important excitatory neurotransmitter in the CNS?

- Glutamate

What is the most important inhibitory neurotransmitter in the CNS?

- GABA

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

- Increase GABA or decrease glutamate

PATHOPHYSIOLOGY OF SEIZURES FOR PHARM

Imbalance of excitatory (ie, glutamate) and inhibitory (ie, GABA) neurotransmitters

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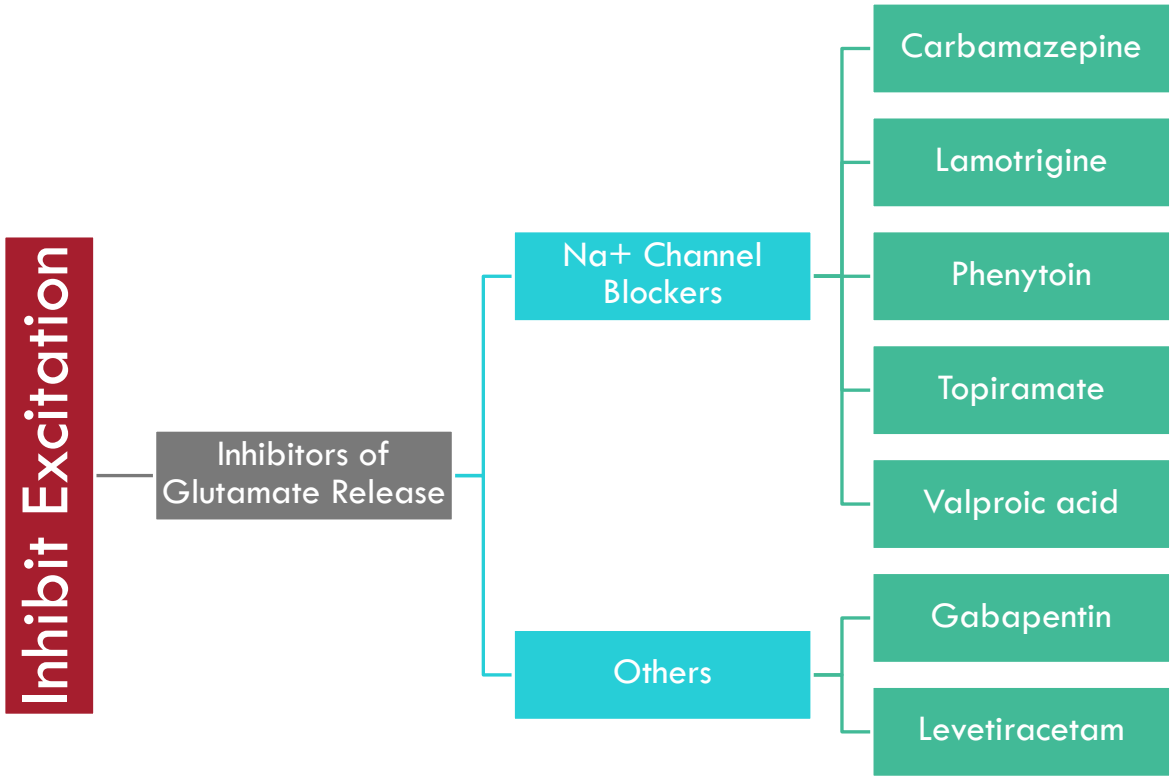
DRUGS FOR SEIZURES

Pharmacology

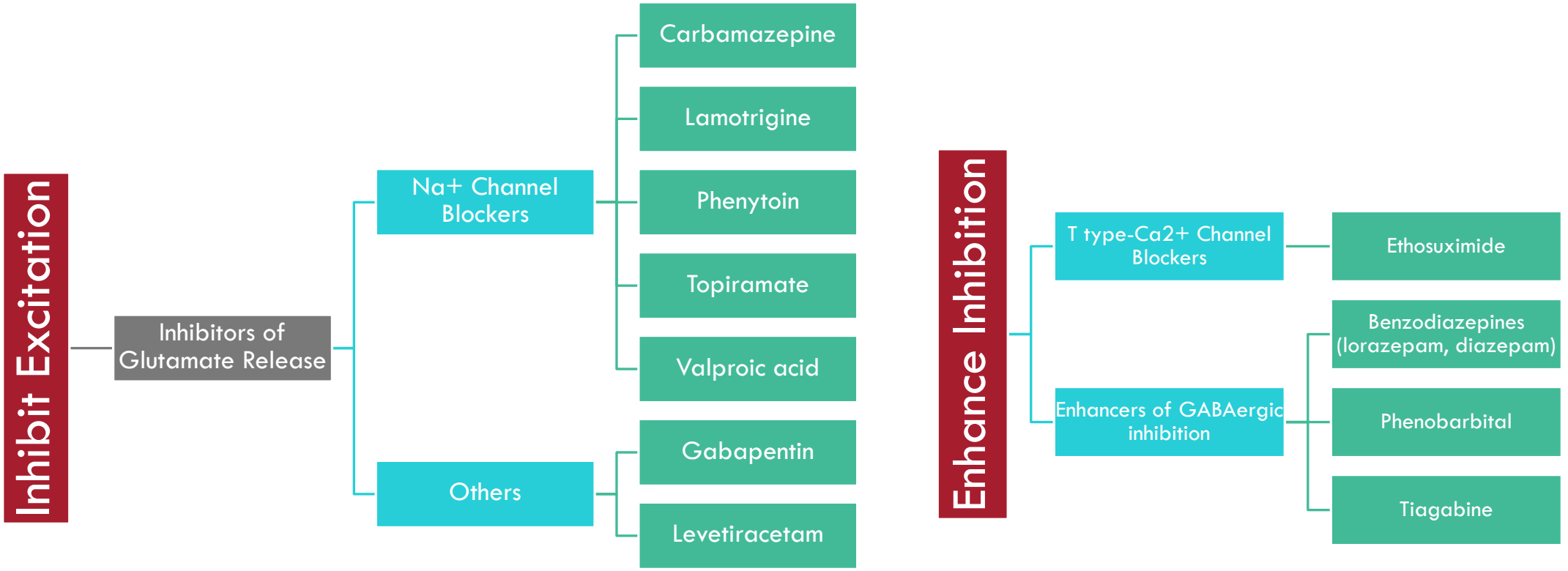
PHARM STRATEGIES FOR SEIZURES

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



PHARMACOLOGIC CONSIDERATIONS

Type of seizure

Pharmacokinetic parameters

Pertinent labs

Medication adherence history

Efficacy

Adverse effects

Potential drug-drug interactions

Cost

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INHIBITORS OF GLUTAMATE RELEASE

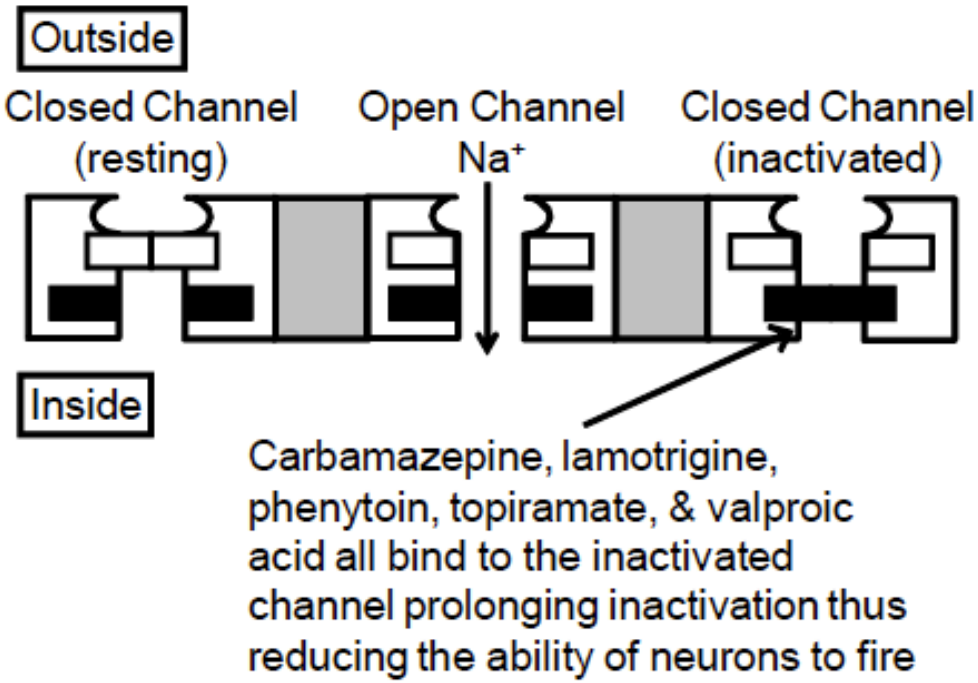
NA+ CHANNEL BLOCKER MECHANISM OF ACTION

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
Carba-mazepine (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

ACTIVE LEARNING

True or false: If the therapeutic index of carbamazepine is low, this means the toxic dose is much higher than the effective dose.

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

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

CARBAMAZEPINE ADME

Metabolized in the liver; metabolite is pharmacologically active

Induces liver enzymes (important drug interactions)

Narrow therapeutic window

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

ACTIVE LEARNING

Drug A is a metabolic inducer of Drug B. Drug B is a metabolic inducer of Drug A. What would you expect to happen to the levels of Drug A and B when given concomitantly?

PHENYTOIN (HYDANTOIN)

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 Enhanced metabolism of oral contraceptives Carbamazepine (enhances metabolism of phenytoin; phenytoin reduces levels of carbamazepine)

PHENYTOIN ADME

Low blood levels displays first-order kinetics

Higher blood levels displays **zero-order kinetics**

- One of very few drugs that exhibits zero-order kinetics

Metabolizing enzymes saturated at blood levels needed to control seizures

- ↑ in phenytoin dose could → disproportionate ↑ in the drug's concentration in the blood → toxicity

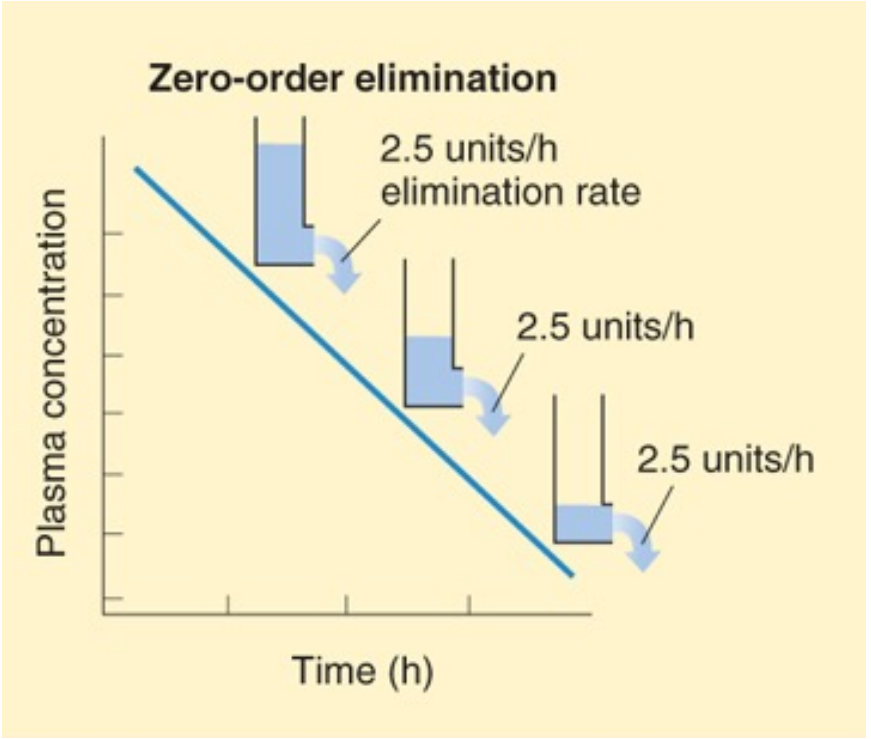


Image from Katzung & Trevor's Pharmacology: Examination & Board Review, 13e; 2021.

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 ↓ phenytoin dose if given with valproic acid.

Dosed in phenytoin equivalents (versus mass)

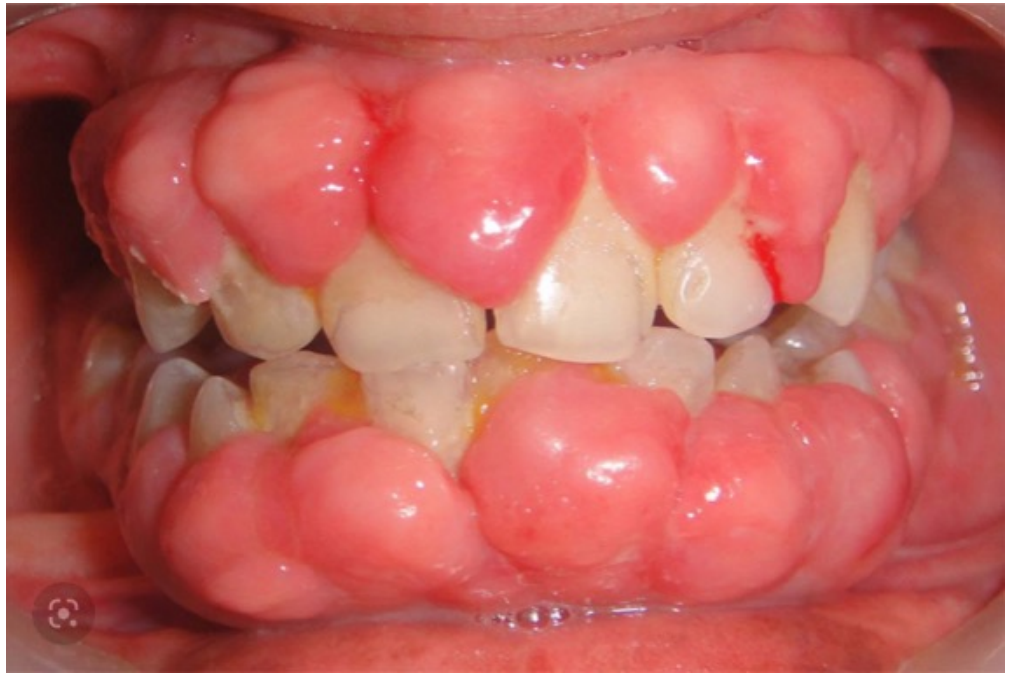
Induces various CYPs

Low water solubility hinders IV use

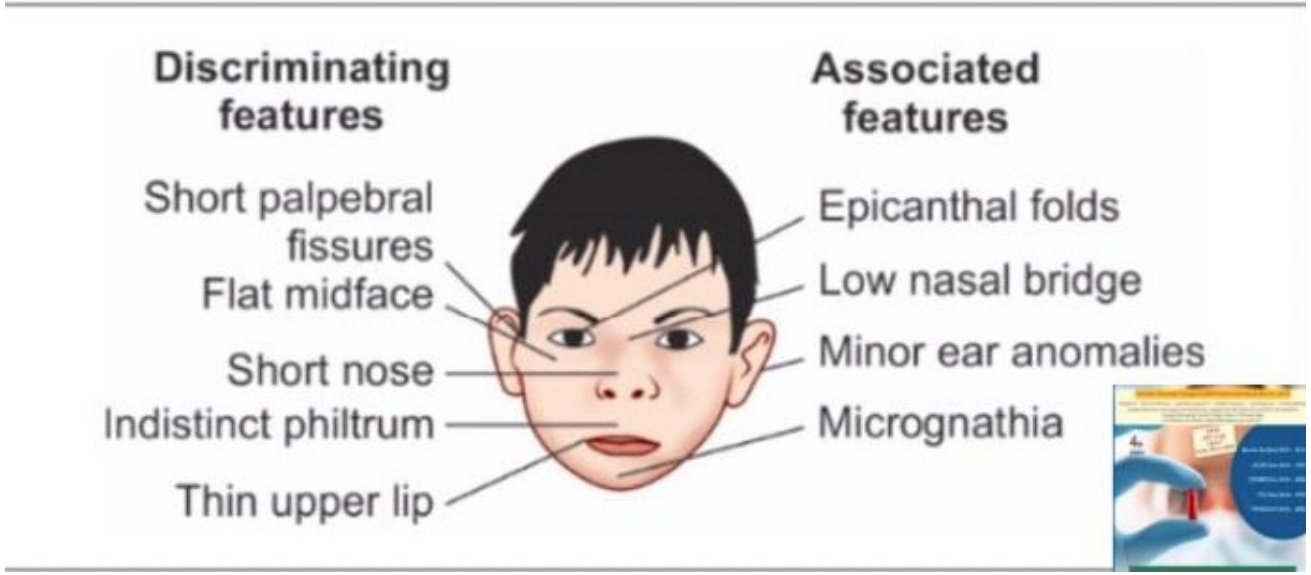
- Fosphenytoin is a water soluble prodrug given IV
- Converted to phenytoin by phosphatases in liver and red blood cells

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

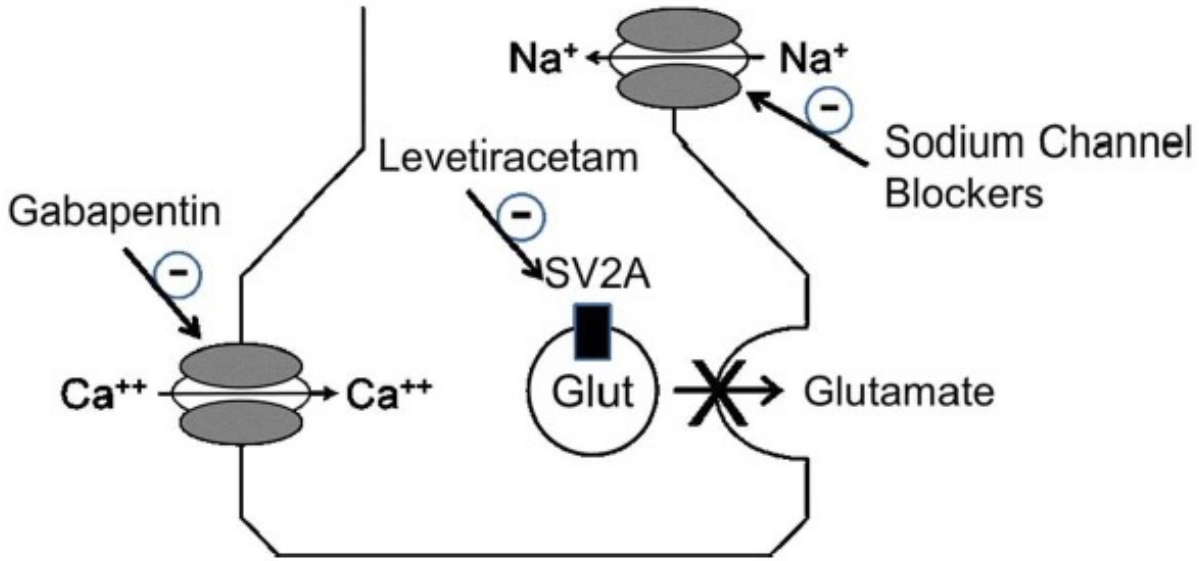
OTHER DRUGS THAT INHIBIT GLUTAMATE RELEASE

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 vesicle ↓ release of glutamate

Gabapentin's mechanism is not entirely understood

- Binds to protein subunit of voltage-gated calcium channels which may ↓ 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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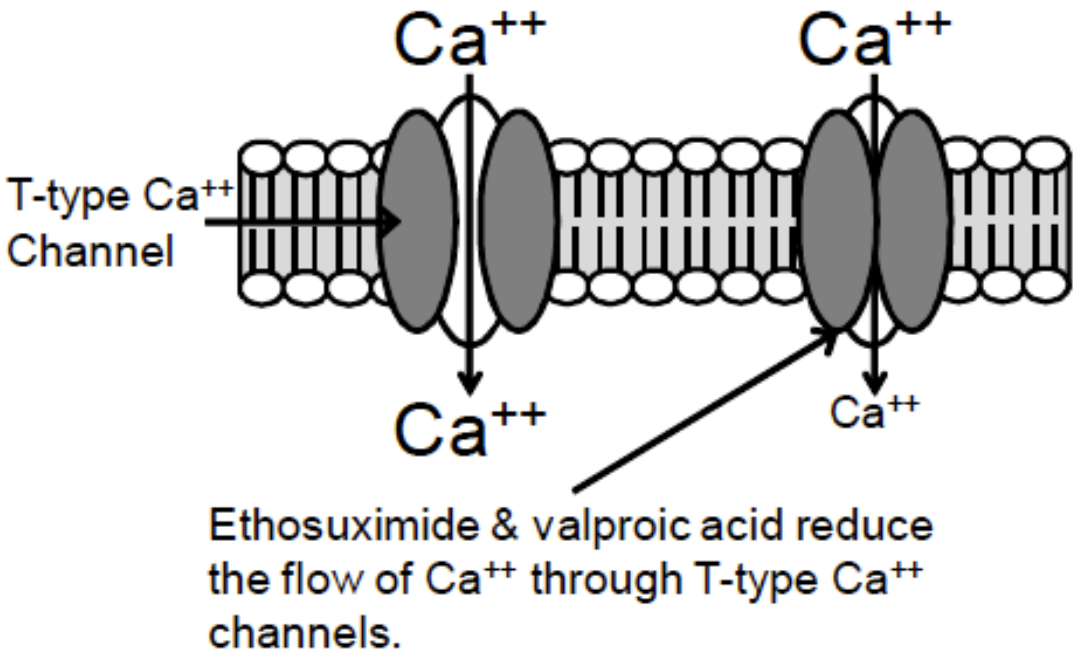
T-TYPE CA2+ CHANNEL BLOCKERS

T-TYPE CA2+ CHANNEL BLOCKER MECHAN. OF ACTION

Reducing the flow of Ca++ through T-type calcium channels ↓ 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

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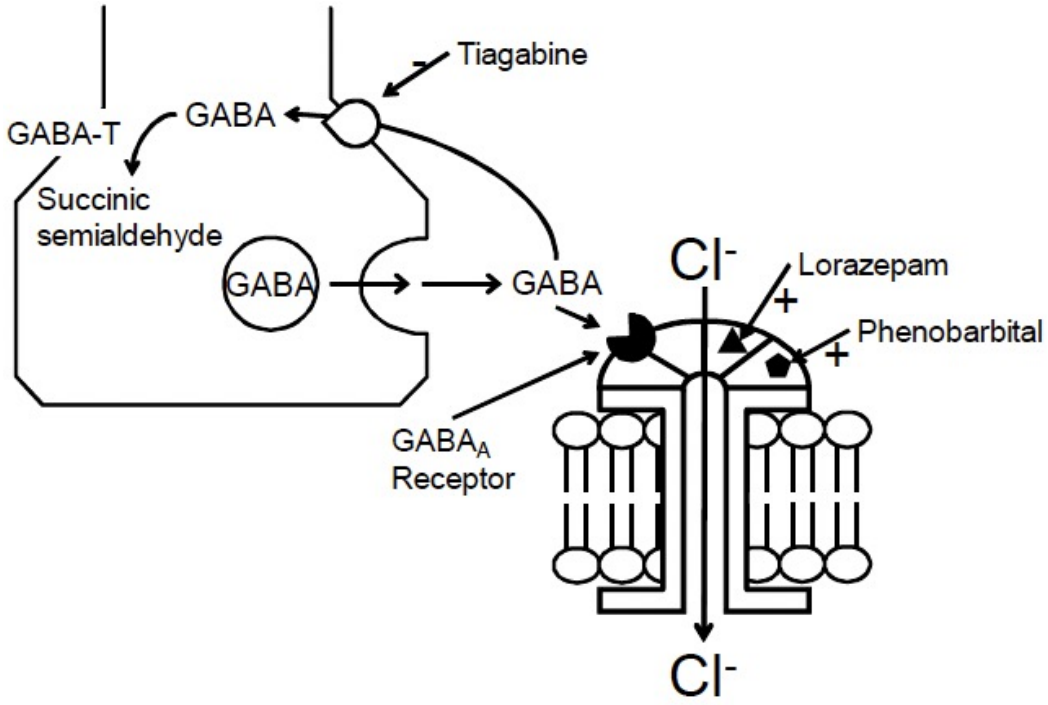
In the presence of GABA, the GABA-A receptor is opened allowing an influx of Cl-,
→ ↑ membrane polarization (hyperpolarization)

ENHANCERS OF GABAERGIC INHIBITION



Tiagabine blocks active reuptake of GABA into the nerve ending → ↑ concentration of GABA in synaptic cleft

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

- Bind to sites oother 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

OTHER DRUGS

Cenobamate

Eslicarbazepine

Cannabidiol

Lacosamide

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ADME SUMMARY

PK PARAMETERS OF INTEREST

Heavily Renally Eliminated AEDs	Heavily Protein Bound AEDs
• Cenobamate (88%) • Eslicarbazepine (66-90%) • Gabapentin (76-81%) • Lacosamide (40-60%) • Levetiracetam (66%) • Pregabalin (90%) • Topiramate (70%) • Vigabatrin (80%)	• Cannabidiol (> 94%) • Carbamazepine (75-90%) • Clobazam (80-90%) • Perampanel (95-96%) • Phenytoin (88-92%) • Tiagabine (96%) • Valproic acid (80-90%)

MODERATE TO STRONG CYP ACTIVITY

CYP2C19 INHIBITION

- Cannabidiol
- Cenobamate

CYP2B6 INDUCTION

- Carbamazepine

CYP3A4 INDUCTION

- Carbamazepine
- Cenobamate
- Eslicarbazepine
- Phenobarbital
- Phenytoin

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SUMMARY OF INDICATIONS/CLINICAL USE

TONIC-CLONIC EPILEPSY MONOTHERAPY

Medication	Evidence
Carbamazepine Lamotrigine Oxcarbazepine Phenytoin Phenobarbital Topiramate Valproic Acid	Level C
Gabapentin Levetiracetam Vigabatrin	Level D

ABSENCE EPILEPSY MONOTHERAPY

Medication	Evidence
Ethosuximide Valproic acid	Level A
Lamotrigine	Level C

Contraindicated

- Carbamazepine
- Oxcarbazepine
- Tiagabine
- Vigabatrin

Avoid due to potential exacerbation of absence seizures

- Phenytoin
- Phenobarbital

Avoid due to ineffectiveness

- Gabapentin
- Pregabalin

STATUS EPILEPTICUS (SE)

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

GENERALIZED CONVULSIVE SE GUIDELINES

Phase	Management
Stabilization Phase (0-5 minutes of seizure activity)	Airway, Breathing, Circulation (ABCs) If glucose < 60 mg/dL, give thiamine followed by dextrose Collect all pertinent labs and start IV fluids
Initial Therapy Phase (5-20 minutes of seizure activity)	**Benzodiazepine (midazolam IM, lorazepam/diazepam IV)** Could give IV phenobarbital, diazepam rectally, or midazolam intranasally/buccally
Second Therapy Phase (20-40 minutes of seizure activity)	**Antiepileptic (IV fosphenytoin/valproic acid/levetiracetam)** Could give phenobarbital IV (or potentially phenytoin IV)

PREGNANCY

Most pregnant patients exposed to AEDs deliver healthy infants

- Fetal exposure to older AEDs associated with congenital anomalies (oral cleft and cardiac, urinary tract and neural tube defects)

All agents should be used in monotherapy at the lowest dose possible

- Risk to offspring is considered to be less than risk of seizures during 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 those using AEDs during pregnancy
- Higher folic acid doses may be needed

PREGNANCY

Potentially Safer AEDs

Lamotrigine and levetiracetam may be safest options in pregnant patients

Concerning AEDs

Valproic acid should be avoided, if possible

- Highly teratogenic, can reduce cognitive outcomes in offspring, linked to polycystic ovarian syndrome

Phenytoin, phenobarbital, carbamazepine, and topiramate during pregnancy is also of concern because of their increased risk for major congenital malformations

MEDICATION CAUSES OF SEIZURES

1. Tramadol
2. Bupropion
3. Theophylline
4. Stimulants (including amphetamines and cocaine)
5. β-lactam antibiotics (particularly carbapenems)
6. Lithium
7. Antidepressants and antipsychotic agents
8. Fluoroquinolones (often with concomitant NSAIDs)
9. Alcohol (both excessive use and withdrawal)

GUIDING YOUR STUDY PRIORITIES

Mechanism of action

Unique adverse effects

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

REFERENCE LIST

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ANY QUESTIONS?