Antiepileptics

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

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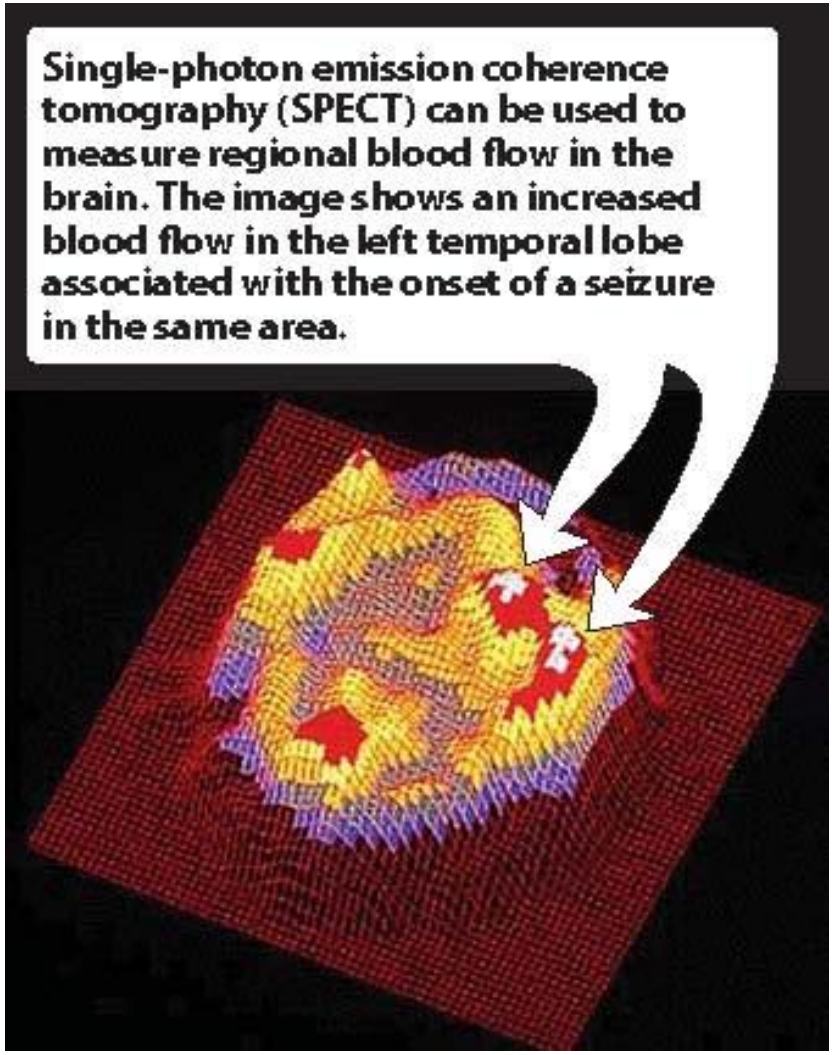
Overview: Epilepsy

- **Seizures**
  - Abnormal excessive neuroactivity in the brain
- **Convulsions**:
  - Rapid, repeated muscle contraction and relaxation resulting from excessive neuroactivity in the brain.
- **Epilepsy:**
  - A neurological disorder of multiple, different seizures resulting from excessive discharge of cerebral neurons.

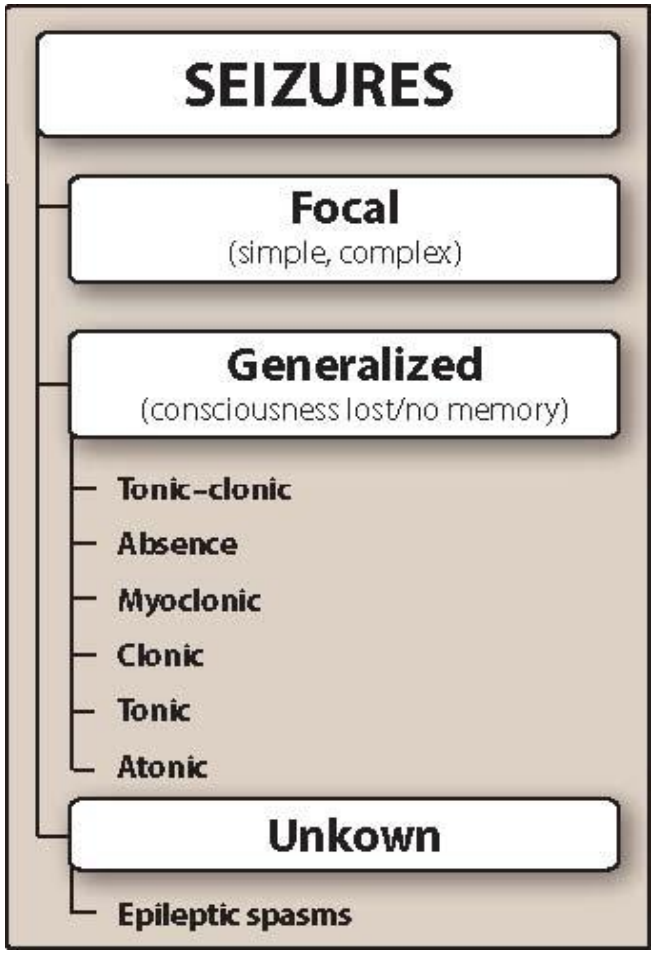


Seizures: Etiology

- Trauma
- Encephalitis
- Drugs
- Withdrawal from depressants
- Tumor
- High fever
- Hypoglycemia
- Extreme acidosis
- Extreme alkalosis
- Hyponatremia
- Hypocalcemia
- Idiopathic

Most cases of epilepsy are idiopathic

Classification of Seizures



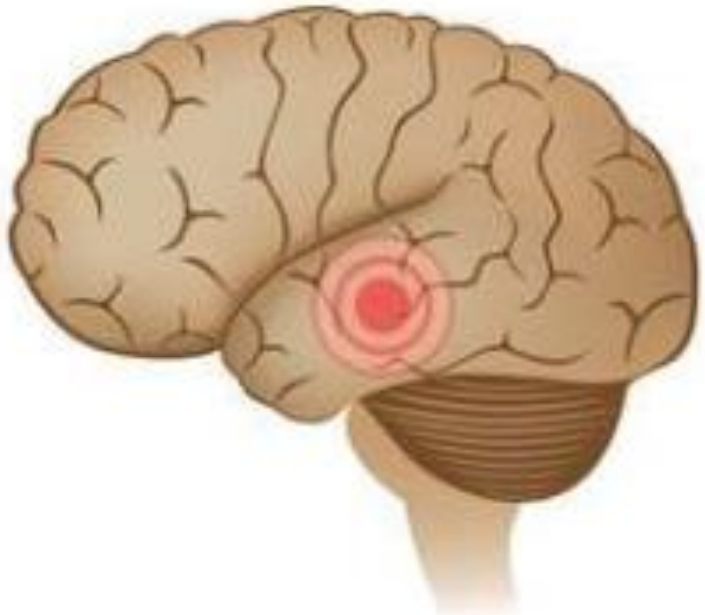
Overview: Epilepsy

- **Focal (partial) seizures:**

- Involves one portion of the brain i.e. one lobe.

- Symptoms depend on the site of discharge “primary focus”.

- Possibility of progressing into a generalized tonic-clonic seizure.



Partial seizure

Focal (partial) seizures:

Simple partial

- Confined to a single locus in the brain
- NO loss of consciousness
- Single muscle group or a limb

Complex partial

- Consciousness is altered
- Motor dysfunction/hallucination /distortion

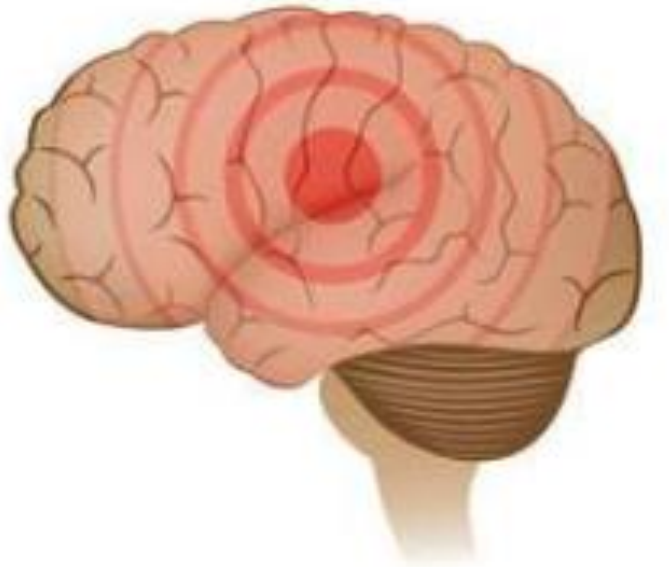
Overview: Epilepsy

- **Generalized seizures:**

- Starts at a focal point and spreads to involve both hemispheres.

- Could be convulsive or nonconvulsive.

- Associated with <u>immediate loss of consciousness.</u>



Generalized seizure

Generalized seizures

Tonic-clonic
- Loss of consciousness
- **Tonic** (continuous contractions) and **clonic** (rapid contraction and relaxation)
- Followed by confusion/exhaustion

Absence
- Brief, abrupt, self-limiting
- Pediatric: 3-5 until puberty
- Starring/rapid-eye blinking
- Characteristic EEG profile

Myoclonic
- Short episodes of muscle contractions i.e., jerks of the limbs

Clonic
- Also brief episodes of muscle contraction similar to myoclonic
- Consciousness is more impaired with clonic

Tonic
- Increased muscle tone
- < 60 seconds

Atonic
- Sudden loss of muscle tone “drop attacks”

Epilepsy: Therapeutic Strategy

- “No cure”
- Complete suppression of seizures, or
- Decrease the number of episodes with minimal side effects.

How?

- Pharmacological
- Ketogenic diet
- Surgery/Vagal Nerve Stimulation
- Correct the underlying cause

Epilepsy: How to select which drug?

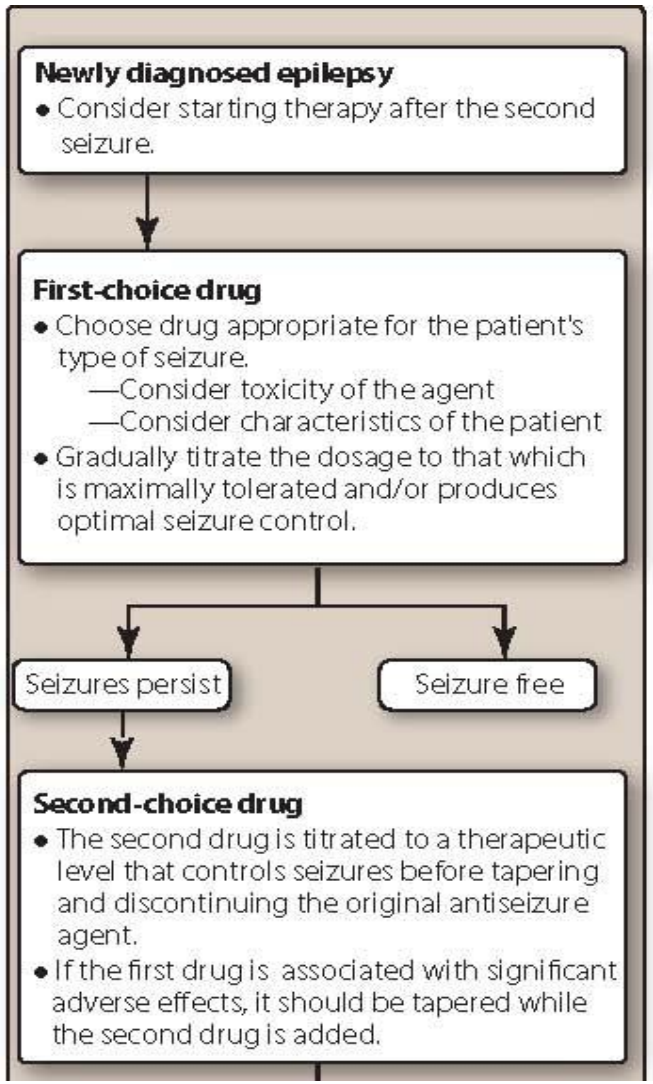
Choice of drug treatment is based on:

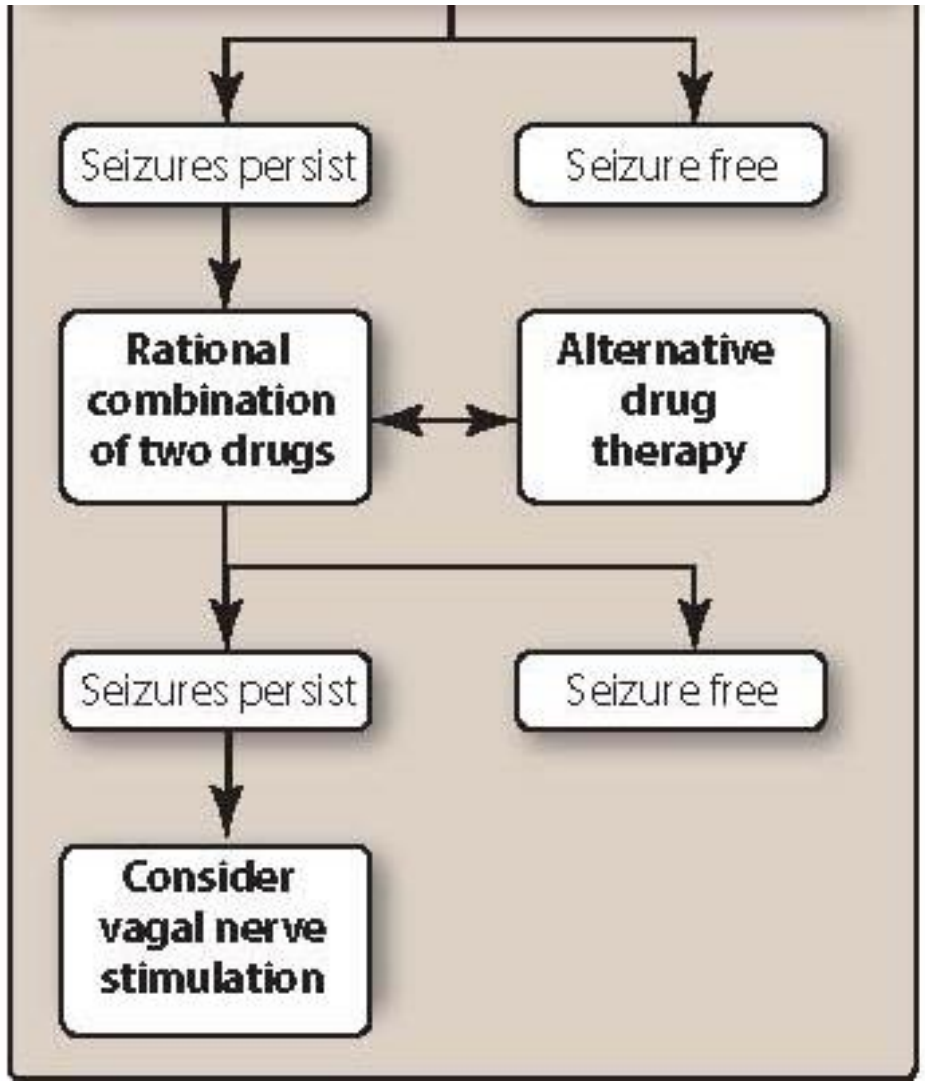
1- type of seizure

2- patient-specific variables (age, comorbidities, lifestyle….)

3- characteristics of the drug (cost, adverse effects, interactions…)

Epilepsy: Therapeutic Strategy





How do antiepilepsy medications work?

Blocking voltage-gated channels (Na^{+} or Ca^{++})

Enhancing inhibitory GABAergic impulses

Interfering with excitatory glutamate transmission

Antiepileptic drugs

Na^+-channels inhibitors

- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Valproic acid
- Lamotrigine
- Topiramate

↑ GABAergic transmission

- Benzodiazepines
- Phenobarbital
- Valproic acid
- Gabapentin?, Pregabalin?
- Felbamate

Ca^{++}-channels inhibitors

- Ethosuximide
- Lamotrigine
- Valproic acid

Others:

- **NMDA receptor blockers**: Felbamate , topiramate
- **AMPA receptor blockers**: Perampanel
- **H-current modulators**: Gabapentin, lamotrigine
- **Carbonic anhydrase inhibitors**: Topiramate, zonisamide
- **Neuronal potassium channel (KCNQ [Kv7]) opener**: Ezogabine

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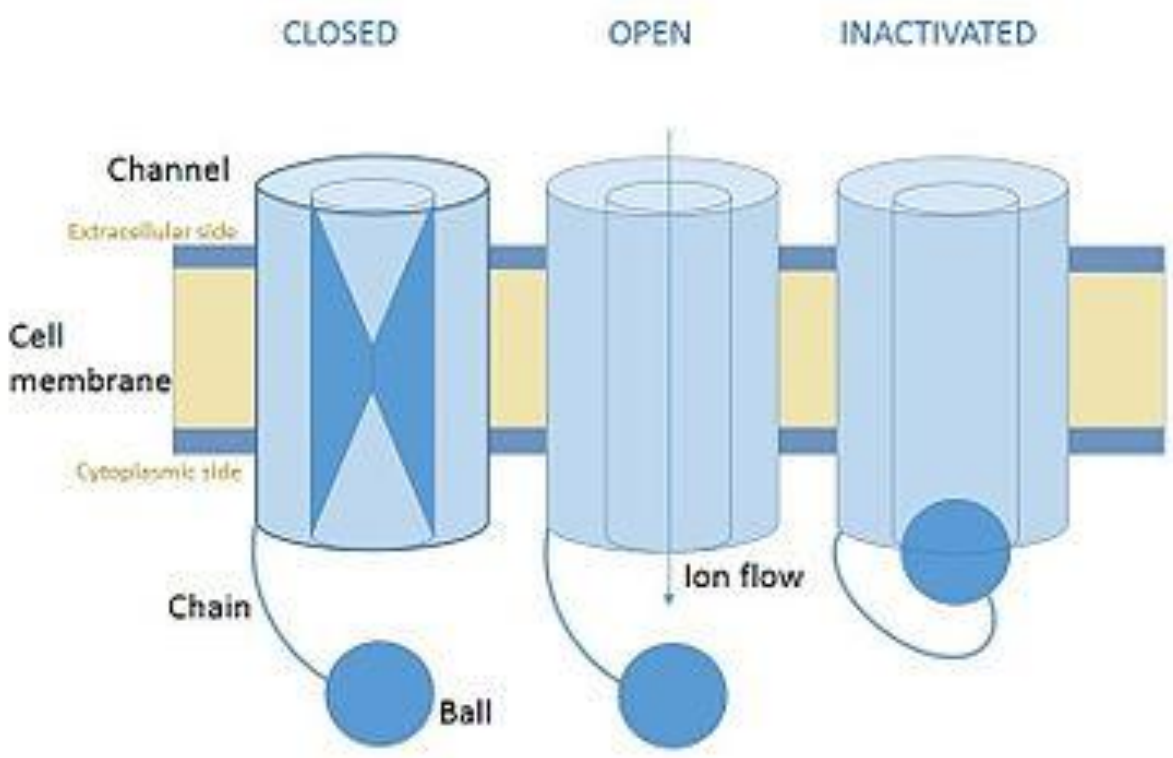
Phenytoin

MOA:

Blocks voltage-gated Na^+ channels by binding to inactive state→ slow recovery



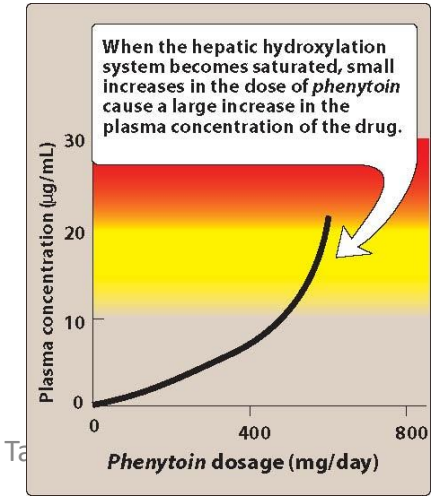
Phenytoin

MOA:

Blocks voltage-gated Na^+ channels by binding to inactive state→ slow recovery

Indications:

- Focal seizures
- Tonic-clonic
- NOT good for absence seizures
- Status epilepticus (after BZD)
- Antiarrhythmic/digoxin toxicity

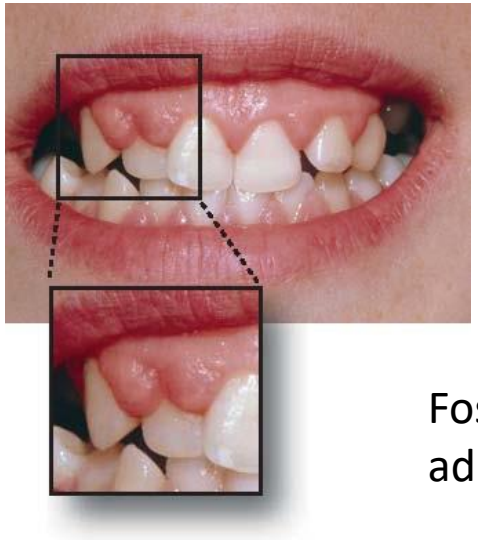


Pharmacokinetics:

- Induces CYP2C, CYP3A, UGT
- "saturable enzyme metabolism"
- Non-linear kinetics
- Toxicity

Adverse effects

- Nystagmus, ataxia
- Diplopia, sedation
- Gingival hyperplasia
- Peripheral neuropathy/osteoporosis
- Teratogenic
- Blood: ↓ folate → Megaloblastic anemia
- Drug-drug interactions: e.g., warfarin



Fosphenytoin for IM administration

Antiepileptic drugs

Na^+-channels inhibitors

- **Phenytoin**
- Carbamazepine
- Oxcarbazepine
- Valproic acid
- Lamotrigine
- Topiramate

↑ GABAergic transmission

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Ca^{++}-channels inhibitors

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- **Neuronal potassium channel (KCNQ [Kv7]) opener**: Ezogabine

Carbamazepine

MOA:

Blocks Na^+ channels

Indications:

- Focal seizures
- Tonic-clonic
- NOT good for absence seizures
- Trigeminal neuralgia
- Bipolar disorder

Pharmacokinetics:

- Absorbed slowly
- Long half-life (~ 30 hours)
- Induces CYP2C, CYP3A, UGT

Adverse effects

- Hyponatremia
- Aplastic anemia
- Teratogenic: Spina Bifida
- Drowsiness; headache; dizziness; nausea

Oxcarbazepine

- Prodrug
- Less side effects

Antiepileptic drugs

Na^+-channels inhibitors

- **Phenytoin**
- **Carbamazepine**
- **Oxcarbazepine**
- Valproic acid
- Lamotrigine
- Topiramate

↑ GABAergic transmission

- Benzodiazepines
- Phenobarbital
- Valproic acid
- Gabapentin?, Pregabalin?
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Ca^{++}-channels inhibitors

- Ethosuximide
- Lamotrigine
- Valproic acid

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- **Neuronal potassium channel (KCNQ [Kv7]) opener**: Ezogabine

Valproic acid

MOA:

- Blocks Na^+ channels
- Blocks GABA transaminase (GABA-T)
- Blocks T-type Calcium channels

Indications:

- Focal seizures
- Generalized seizures
- Absence seizures
- Bipolar disorder

Pharmacokinetics:

- Inhibits CYP2C9, UGT, epoxide hydroxylase

Adverse effects

- Hepatotoxicity
- Teratogenicity
- CNS-related

Valproic acid

vs

Sodium valproate

vs

Divalproex sodium

Antiepileptic drugs

Na^+-channels inhibitors

- **Phenytoin**
- **Carbamazepine**
- **Oxcarbazepine**
- **Valproic acid**
- Lamotrigine
- Topiramate

↑ GABAergic transmission

- Benzodiazepines
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Ca^{++}-channels inhibitors

- Ethosuximide
- Lamotrigine
- **Valproic acid**

Others:

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Lamotrigine

MOA:

- Blocks Na^{+} channels
- Blocks voltage-gated Ca^{++} channels

Adverse effects

- CNS-related side effects
- Severe skin reaction (life-threatening)

Indications:

- Focal seizures
- Generalized seizures
- Absence
- Lennox-Gastaut syndrome
- Bipolar disorder

Pharmacokinetics:

- Metabolized by UGT
- What will happen when combined with *phenytoin*? *Valproic acid*?

Antiepileptic drugs

Na^+-channels inhibitors

- **Phenytoin**
- **Carbamazepine**
- **Oxcarbazepine**
- **Valproic acid**
- **Lamotrigine**
- Topiramate

↑ GABAergic transmission

- Benzodiazepines
- Phenobarbital
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- Gabapentin?, Pregabalin?
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Ca^{++}-channels inhibitors

- Ethosuximide
- **Lamotrigine**
- **Valproic acid**

Others:

- **NMDA receptor blockers**: Felbamate , topiramate
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- **H-current modulators**: Gabapentin, **lamotrigine**
- **Carbonic anhydrase inhibitors**: Topiramate, zonisamide
- **Neuronal potassium channel (KCNQ [Kv7]) opener**: Ezogabine

Topiramate

MOA:

- Blocks Na^+ channels
- Blocks L-type Calcium channels
- Carbonic anhydrase inhibitor
- NMDA blocker

Adverse effects

- Somnolence
- Weight loss
- Paresthesia
- Renal stones
- Oligohidrosis
- hyperthermia

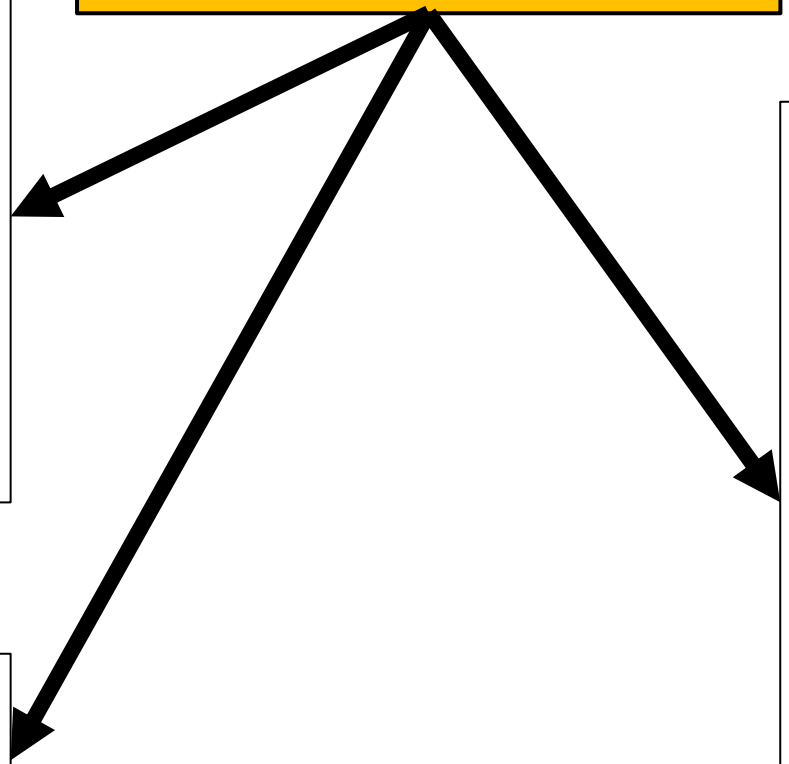
Indications:

- Focal seizures
- Generalized seizures
- Migraine prevention

Pharmacokinetics:

- Inhibits CYP2C9

Zonisamide



MOA:

- Blocks Na^+ channels
- Blocks T-type Calcium channels
- Limited carbonic anhydrase inhibitor

Indications:

- Focal seizures

Adverse effects

- CNS adverse effects
- Nephrolithiasis
- Oligohidrosis
- Contraindicated in patients with sulfonamide hypersenesitivity

Antiepileptic drugs

Na^+-channels inhibitors

- **Phenytoin**
- **Carbamazepine**
- **Oxcarbazepine**
- **Valproic acid**
- **Lamotrigine**
- **Topiramate**

Ca^{++}-channels inhibitors

- Ethosuximide
- **Lamotrigine**
- **Valproic acid**

↑ GABAergic transmission

- Benzodiazepines
- Phenobarbital
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- **Carbonic anhydrase inhibitors**: **Topiramate**, zonisamide
- **Neuronal potassium channel (KCNQ [Kv7]) opener**: Ezogabine

Ethosuximide

MOA:

- Blocks T-type Calcium channels

Indications:

- Absence seizure only

(Drug of choice)

Pharmacokinetics:

- Half-life: 30-60 hrs

Antiepileptic drugs

Na^+-channels inhibitors

- **Phenytoin**
- **Carbamazepine**
- **Oxcarbazepine**
- **Valproic acid**
- **Lamotrigine**
- **Topiramate**

Ca^{++}-channels inhibitors

- **Ethosuximide**
- **Lamotrigine**
- **Valproic acid**

↑ GABAergic transmission

- Benzodiazepines
- Phenobarbital
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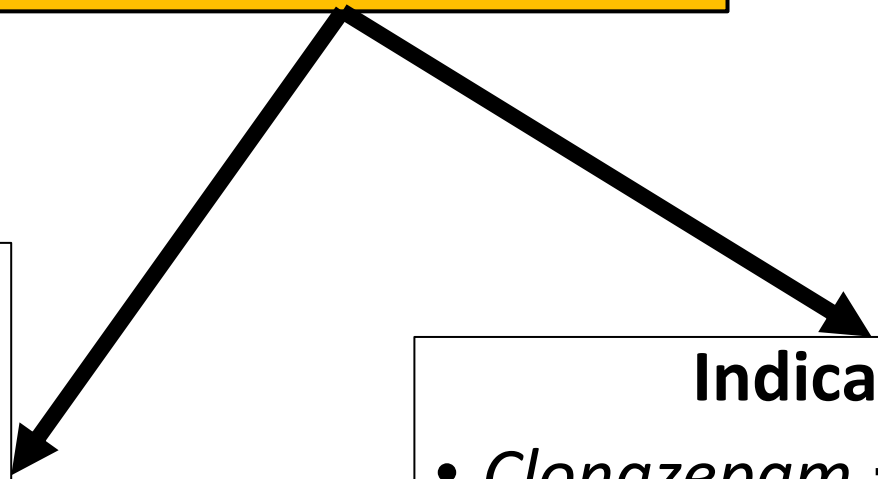
Benzodiazepines Phenobarbital



MOA:

- Bind to $GABA_A$ receptors and enhance GABA binding → facilitates Cl^- entry → inhibitory

Indications:

- *Clonazepam* → adjunctive antiseizure therapy
- *Diazepam* → status epilepticus (drug of choice)

Antiepileptic drugs

Na^+-channels inhibitors

- **Phenytoin**
- **Carbamazepine**
- **Oxcarbazepine**
- **Valproic acid**
- **Lamotrigine**
- **Topiramate**

Ca^{++}-channels inhibitors

- **Ethosuximide**
- **Lamotrigine**
- **Valproic acid**

↑ GABAergic transmission

- **Benzodiazepines**
- **Phenobarbital**
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- **Neuronal potassium channel (KCNQ [Kv7]) opener**: Ezogabine

Gabapentin
Pregabalin

MOA:

- Analog of GABA
- It does NOT act at GABA receptor
- MOA is unknown

Adverse effects

- Sedation
- Euphoria

Indications:

- Adjunct therapy for focal seizures
- Neuropathic pain, e.g., postherpetic neuralgia, diabetic neuropathy

Pharmacokinetics:

- Secreted unchanged
- Few drug interactions
- Suitable for elderly

Antiepileptic drugs

Na^+-channels inhibitors

- **Phenytoin**
- **Carbamazepine**
- **Oxcarbazepine**
- **Valproic acid**
- **Lamotrigine**
- **Topiramate**

Ca^{++}-channels inhibitors

- **Ethosuximide**
- **Lamotrigine**
- **Valproic acid**

↑ GABAergic transmission

- **Benzodiazepines**
- **Phenobarbital**
- **Valproic acid**
- **Gabapentin?, Pregabalin?**
- Felbamate

Others:

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Felbamate

MOA:

- Blocks voltage-gated Na^+ channels
- Blocks NMDA receptors
- Blocks Ca^{++} channels
- Potentiates GABA

Adverse effects

- Aplastic anemia
- Hepatic failure
- Dangerous drug

Indications:

- Reserved for refractory epilepsy
- Lennox-Gastaut syndrome

Pharmacokinetics:

- Inhibits CYP2C19
- Induces CYP3A4

Antiepileptic drugs

Na^+-channels inhibitors

- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Valproic acid
- Lamotrigine
- Topiramate

↑ GABAergic transmission

- Benzodiazepines
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Ca^{++}-channels inhibitors

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- **Carbonic anhydrase inhibitors**: **Topiramate**, zonisamide
- **Neuronal potassium channel (KCNQ [Kv7]) opener**: Ezogabine

Ezogabine

MOA:

- Open voltage-gated M-type potassium channels → stabilizing resting membrane potential

Adverse effects

- Urinary retention
- QT interval prolongation
- Blue skin discoloration
- Retinal abnormalities

Pharmacokinetics:

- No drug interactions at low doses

Levetiracetam

MOA:

- unknown

Indications:

- Focal (simple and complex) seizures
- Adjunct therapy for generalized seizures

Adverse effects

- Dizziness
- somnolence

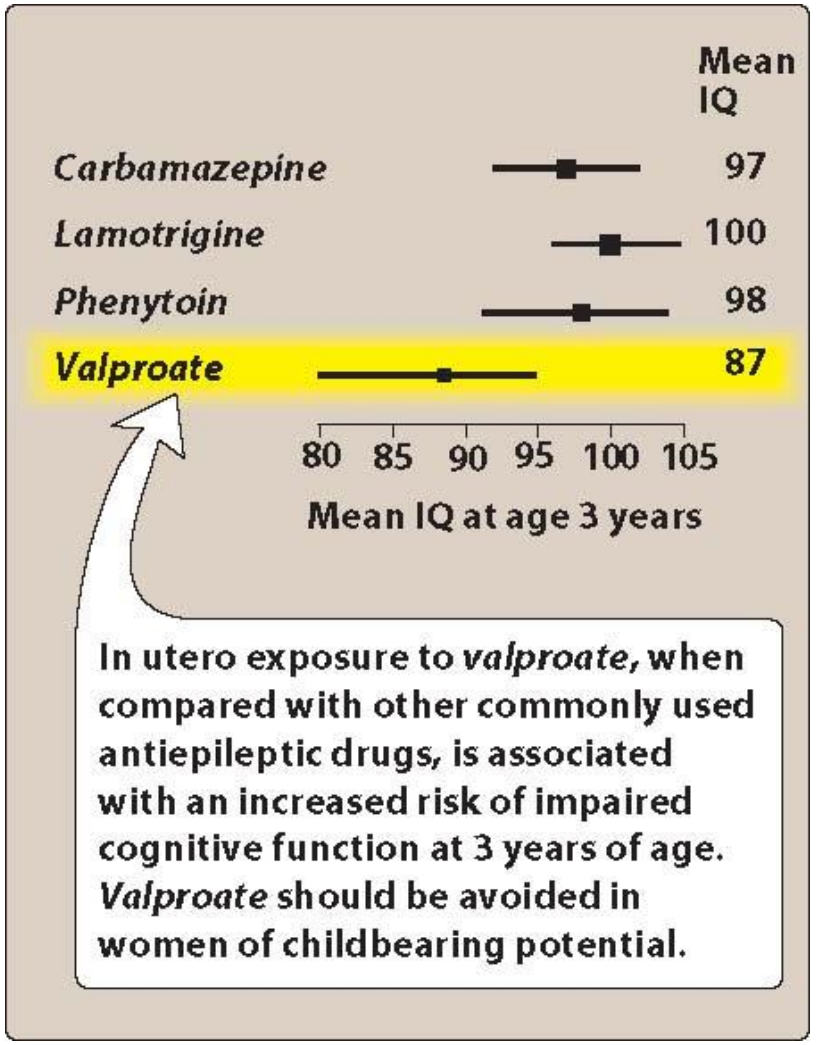
Status Epilepticus

- *Continuous or repetitive seizures (> 20 min) with impaired consciousness during the interictal period.*
- **Management**

1. **Diazepam** (IV or rectal) → for rapid control.
2. **Fosphenytoin** (prodrug) or **phenytoin**→ long-acting, to maintain control.
3. **Phenobarbital**→2nd choice to phenytoin.
4. **Propofol** (IV anesthesia)→ in resistant cases.

Antiepileptics during pregnancy

- Monotherapy
- The lowest possible dose
- Lamotrigine; gabapentin = safe
- Valproic acid; phenobarbital; phenytoin, others = contraindicated
- *Cleft lip*, *neural tube defect* (patients considering pregnancy while on antiepileptics should receive folic acid supplements)



AAN Guidelines for Epilepsy Treatment

Level	Recommendation
Level B	LTG use should be considered to decrease seizure frequency.
Levels B and Level C	LTG use should be considered (**Level B**) and GBP use may be considered (**Level C**) to decrease seizure frequency in patients aged ≥60 years.
Level C	LEV use may be considered to decrease seizure frequency.
Level C	ZNS use may be considered to decrease seizure frequency.
Level C	VGB use appears to be less efficacious than immediate-release carbamazepine (CBZ) use and may not be offered; furthermore, toxicity profile precludes VGB use as first-line therapy.
Level C	PGB use at 150 mg/d is possibly less efficacious than LTG use at 100 mg/d.
Level U	Evidence is insufficient to consider GBP, OXC, or TPM instead of CBZ.
Level U	Evidence is insufficient to consider TPM instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic (GTC) seizures, or generalized epilepsy (GE) presenting with GTC seizures.
Level U	Data are lacking to support or refute use of third-generation AEDs, CLB, FBM, or VGB in treating new-onset epilepsy.
Level U	Data are lacking to support or refute use of newer AEDs in treating unclassified GTC seizures.

Recommendation for childhood absence epilepsy

Level	Recommendation
Level B	Unless there are compelling reasons based on adverse events (AEs) profile, ethosuximide (ETS) or VPA use should be considered before LTG use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy.

Figure 12.4 in chapter 12 is very important

Summary of Therapeutic Strategy

Proper diagnosis

Monotherapy

Start with ***a small dose*** and **a single drug** then gradually increase the dose

Termination of therapy:

- After 2 years (no fits)
- Gradually

Pregnancy:

- Least effective dose of least teratogenic drug
- Folic acid supplements

Consider monitoring of serum drug levels

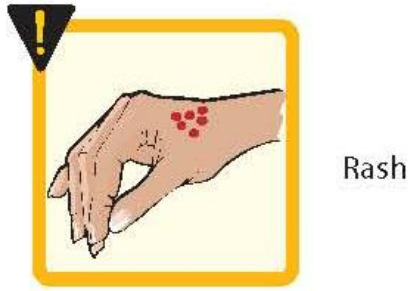
DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
Carbamazepine	Blocks Na^+ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
Eslicarbazepine acetate	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Ethosuximide	Blocks Ca^{2+} channels	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.
Ezogabine	Enhances K^+ channels	Urinary retention, neuropsychiatric symptoms, dizziness, somnolence, QT prolongation, reports of blue skin discoloration, and retina changes.
Felbamate	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.
Lacosamide	Multiple mechanisms of action	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
Lamotrigine	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.
Levetiracetam	Multiple mechanisms of action	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Perampanel	Blocks AMPA glutamate receptors	Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls, long half-life.
Phenytoin	Blocks Na^+ channels	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (*fosphenytoin*).
Pregabalin	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination.
Rufinamide	Unknown	Shortened QT interval. Multiple drug interactions.
Tiagabine	Blocks GABA uptake	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	Multiple mechanisms of action	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Vigabatrin	Irreversible binding of GABA-T	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
Zonisamide	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.

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	✔

*Low = 60% or less, Moderate = 61%-85%, High = >85%; ^Newly approved. Limited data in patients available. **Prodrug.

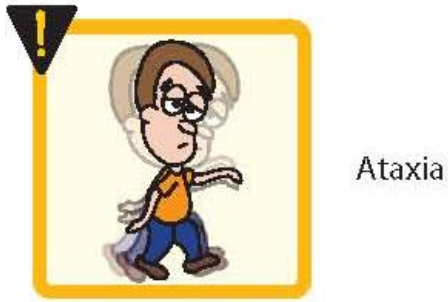
Name an AED that is associated with each of the following adverse effects

Phenobarbital

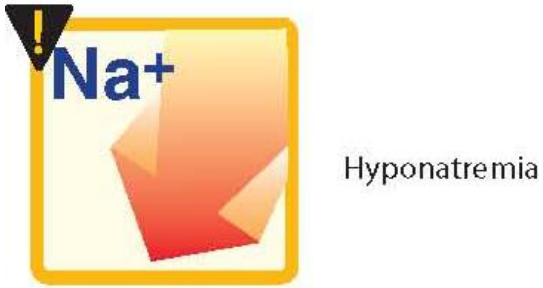


Lamotrigine

Topiramate



Phenytoin



Carbamazepine

Valproic acid

Several classes of antiepileptic drugs (AEDs) interfere with the propagation of action potentials in hyperactive epileptic foci by inhibiting the activation of voltage-gated Na+ channels. All of the following medications share this mechanism of action, EXCEPT:

A) Zonisamide
B) Carbamazepine
C) Conazepam
D) Valproic acid
E) Phenytoin

All of the following mechanisms of action account for the antiepileptic effects of the drug topiramate, EXCEPT:

a) Voltage-gated Na+ channel blockade
b) L-type Ca++ channel blockade
c) Carbonic anhydrase inhibition
d) Glutamate NMDA receptor antagonist
e) Facilitation of Cl- influx at GABA receptor

A 25-year-old woman with generalized epilepsy is well controlled on valproate. She indicates that she is interested in becoming pregnant in the next year. With respect to her antiseizure medication, which of the followings should be considered?

a) Leave her on her current therapy and start folic acid supplaments.
b) Consider switching to lamotrigine.
c) Consider adding another antiseizure drug.
d) Decrease her valproate dose

A 52-year-old man has had several focal seizures with impaired consciousness over the last year. Which is the most appropriate initial therapy for this patient?

a) Ethosuximide
b) Levetiracetam
c) Diazepam
d) Phenytoin/Carbamazepine combination