

Seizure vs. Epilepsy

Seizure: high electrical discharge from an area of the CNS (foci), they are one and done, and there is usually a reason such as: vascular, infection, trauma, autoimmune, metabolic disorders, neoplasm, or idiopathic.

Epilepsy: two or more seizures that do not resolve (they may become chronic) there is no VITAMIN reason.

Types of Epileptic Seizures

Focal/Partial Seizures	Simple
	Complex
Generalized Seizures	Generalized tonic-clonic: grand mal seizure, LOC, convulsions, muscle rigidity
Absence	usually in children, brief loss of consciousness, blanks out, stares off into space.
Myoclonic	sporadic (isolated), jerking movements
Clonic	Repetitive, jerking movements
Tonic	Muscle stiffness, rigidity
Atonic	drop seizures, loss of muscle tone

Epileptic "Spasms"

Benign Rolandic	Twitching, numbness, or tingling or one side of tongue/face
West Syndrome	Infantile wiggles
	"JackKnife" seizures (legs fly up)
	Leads to autism or intellectual disabilities later in life.

Epileptic "Spasms" (cont)

Lennox-Gastaut Syndrome	Multiple seizures every day (18-20)
	Cannabis may eliminate these seizures.

Carbamazepine (Tegretol) (Carbatrol, Equetro)

Class:	Na ⁺ Channel blocker
MOA:	Blocks Na ⁺ channel blocker, a tricyclic compound (similar structure to TCA, no high affinity for MAO)
Indications:	Generalized or focal seizures *one of the most widely used, mostly for focal seizure. 1st line treatment for trigeminal neuralgia.
Formulations:	Carbatrol and Equetro (ER capsule), tablet, Tegretol (suspension), chewable tablet, XR tablet
	Not a controlled substance
Side Effects:	N/V, dizziness, blurry vision, diplopia, sedation at high doses, benign leukopenia.
Serious ADRs:	Hyponatremia, Bone marrow suppression, SJS/TEN, osteomalacia, hepatotoxicity (very rare). Rash and hyponatremia are most common reasons for discontinuation. May worsen myoclonic seizures.

Drug Interactions:

	Potent CYP inducer
	Induces CYP3A4, 2C9, 2C19, PgP (will decrease levels of drugs metabolized by these)

Carbamazepine (Tegretol) (Carbatrol, Equetro) (cont)

	Substrate of CYP3A4, 2C8, PgP
	VPA and Lamotrigine can increase carbamazepine levels
	Do not use with hormonal contraception (decreases efficacy of BC)
Considerations:	requires lab monitoring, can induce its own metabolism so levels may decrease over time. Not a sedative so a good choice if that is a concern.

Oxcarbazepine

Class:	Na ⁺ channel blocker
MOA:	Na ⁺ channel blocker, less potent than carbamazepine. Pro-drug for S+licarbazepine
Indications:	adjunct therapy for partial seizures
Formulations:	tablet, oral suspension, ER tablet (Oxtellar XR)
	Not a controlled substance
Side Effects:	may have less than carbamazepine but similar, higher risk of hyponatremia
Considerations:	Less drug interactions than carbamazepine, check Na ⁺ levels
	weak CYP3A4 inducer , does not auto-induce metabolism like carbamazepine

Phenytoin (Dilantin)

Class:	Na ⁺ Channel blocker
MOA:	Na ⁺ Channel blocker (works similarly to Carbamazepine) oldest non-sedating epileptic drug
Indications:	focal (partial) onset seizure, generalized onset seizure (NOT first line), Status Epilepticus
Formulations:	capsule, injection, oral suspension, chewable tablet
	Not a controlled substance
Side Effects:	Hirsutism, sedation, gingival hyperplasia (enlarged gums),
	TOXIC EFFECTS: nystagmus, diplopia, ataxia
Serious ADRs:	SJS/TEN (especially asian), osteomalacia, peripheral neuropathy, tissue necrosis when IV, arrhythmias
Considerations:	may worsen other seizure types (absence, juvenile myoclonic, Dravet's syndrome) When switching formulations keep in mind different dosage forms contain different amounts of PHT (ex. caps and injection are 92% and susp. and chewable tablets are 100%)

Phenytoin (Dilantin) (cont)

Drug Interactions:	Extensively bound to albumin, free PHT is what is active. Drug or conditions that alter albumin will affect PHT levels. Many drugs compete with bound PHT and may cause displacement and lead to toxicity. Patients with liver disease, hypoalbuminemia, or renal failure can lead to abnormally high levels of PHT (toxic levels)
	Metabolized by CYP2C19 and 2C9, induces 3A4, 2C9, 2C19, and 1A2.
	Potent CYP inducer
	Substrate and inducer of P-gP and interacts with most oral contraceptives (decreases efficacy)
Lab monitoring	Free phenytoin levels should be checked in patients with hypoalbuminemia and renal failure. If you can't check free, check total and use given equations to adjust.
Therapeutic Levels	Total 10-20 mg/L Free 1-2.5 mg/L Toxic >30 mg/L Lethal level >100 mg/L

Phenytoin (Dilantin) (cont)

	Draw levels within 2-3 days of starting therapy and then get second level within 5-8 days of therapy initiation and with subsequent dose adjustments
	In stable patients, can draw levels at 3-12 month intervals
	Phenytoin kinetic are non linear -> a small dose increase may cause a BIG increase in plasma concentration

Fosphenytoin (Cerebyx)

Class:	Na ⁺ Channel blocker
Indication:	Same as phenytoin, preferred over phenytoin for parenteral administration if needed.
	Still prefer Benzos in SE because of delayed effects
Formulations:	injection
	not a controlled substance
Side Effects:	same as phenytoin
Drug Interactions:	same as phenytoin
Special Notes:	a prodrug of phenytoin (each mL = 50mg of phenytoin equivalents)

Take Home Points

Skin rashes/hypersensitivities (SJS, TEN, rash)- highest risk with: lamotrigine, phenytoin, carbamazepine, phenobarbital

Take Home Points (cont)

DO NOT USE VPA in women of childbearing age, especially if they are not on effective birth control

Phenytoin levels need to be checked.

Safer pregnancy option: lamotrigine, levetiracetam (Use as monotherapy when at all possible. Pregnancy can lower drug levels so dose adjustments may be required)

Most of the medications decrease effectiveness of hormonal contraceptives.

Therapy is seizure and patient specific.

If a patient doesn't respond to monotherapy, those meds with similar MOAs will likely not be effective so choose another med as adjunct.

Some medications are chosen due to comorbidities.

VPA is mood disorder or migraine.

Pregabalin in neuropathic pain

Epileptic Spasms

Benign Rolandic Lamotrigine

West Syndrome Vigabatrin

Lennox-Gastaut Syndrome Valproate

Topiramate

Lamotrigine

Cannabidiol

If really refractory
Felbamate

Adverse Reactions

SJS Ethosuximide

Carbamazepine

Lamotrigine

Cardio/Respiratory Depression Benzos

Barbiturates

Propofol

Hepatotoxicity Valproate

Adverse Reactions (cont)

Carbamazepine

Felbamate

Barbiturates

Pathophysiology of Seizure

Overactive glutamate in the brain (over excitation) that continues to cause **Na⁺ and Ca²⁺** influx leading to continuous action potentials and stimulation.

To improve that we want to increase actions of GABA which is inhibitory, and decreases the effects of Glutamate.

We can work on the voltage gated channels, directly on GABA, etc.. to decrease seizure activity.

Seizures can be provoked or unprovoked. **Provoked** could be due to electrolyte disturbances, infection, TBI, inflammation, fever, toxicities, etc. **Unprovoked** could be epilepsy (genetic or chronic pathologic process)

Three Major Seizure Patterns

Focal One area of the cortex, isolated to motor or sensory.

With or without loss of consciousness

Generalized starts in a foci and spreads over the entire cortex.

Epileptic "Spams" Benign Rolandic (around the central sulcus)

West Syndrome

Lennox-Gastaut's Syndrome

Overview of How These Drugs Work

Ultimate goal is to inhibit the local generation of seizure discharges to reduce the ability of neurons to fire at high rate and reduced neuronal synchronization.

Modulate Na⁺, Ca²⁺, or K⁺ channels

Overview of How These Drugs Work (cont)

Enhance fast acting GABA-mediated synaptic inhibition (we want to increase overall inhibition, increase GABA)

Modification of synaptic release processes (sv2A, alpha2delta-1)

Diminishing effects of fast glutamate mediated excitation (decreases excitatory effects, decreased Glutamate)

Lamotrigine

MOA: Na⁺ Channel blocker

Indications: adjunct for Lennox-Gastaut syndrome, adjunct for generalized tonic-clonic, mono or adjunct for focal seizures.

Formulations: tablet, chewable tablet, titration kits as well

not a controlled substance

Side Effects: sometimes insomnia instead of sedation, dyspepsia, peripheral edema, HA, dizziness, rash

Serious ADRs: Fatal Rash (SJS) worsened if combined with VPA use

Drug Interactions: VPA greatly increases levels of drug, increased SJS risk. OCPs or other estrogen containing medications reduce lamotrigine levels and may increase seizure occurrence.



Lamotrigine (cont)

Special Notes: normally well tolerated and widely used, safer in pregnancy than others due to lower fetal risk. Rash (as a hypersensitivity) can be reduced by a slow titration of the dose (children at higher risk)

Valproic Acid (Depakene)

MOA: exact mechanism unknown, has broad spectrum efficacy (multiple seizure types)

Indications: generalized tonic-clonic, focal (may not be as effective as carbamazepine/phenytoin) absence, myoclonic (juvenile myoclonic), atonic/akinetic (Lennox-Gastaut)

Formulations: capsule, DR sprinkle, oral solution, IV, DR tablet, ER tablet

Not a controlled drug

Side effects: N/V. GI pain and heartburn (Divalproex has lowest GI risk), weight gain, tremor (dose related) OP

Drug Interactions: a CYP inhibitor of metabolism (will increase levels of phenobarb and ethosuximide) displaces phenytoin from albumin so increasing free phenytoin levels (toxicity). Increases levels of lamotrigine by inhibiting its clearance.

Valproic Acid (Depakene) (cont)

Warnings: **Do not use in women of childbearing age, VPA induced hepatic failure** (children <2 at most risk) The worst teratogen.

Highly protein bound like phenytoin

Initial dosing of 15 mg/kg recommended with slow titration up to a therapeutic dose.

Therapeutic levels are usually anywhere from 50-100 mcg/mL

VPA

Valproic Acid toxicity

L-carnitine (Levocarnitine) Amplified by the liver toxicity

Clinical
 GI: Nausea and vomiting
 CNS: Sedation, ataxia, coma, respiratory depression, tremor, cerebral edema
 Cardiac: Cardiac arrest
 Other: Hyperammonemia, hypernatremia, hypocalcemia, metabolic acidosis

Overdose rarely results in death

Management
 GI decontamination: Activated charcoal
 Naloxone: Unclear mechanism, case reports show success
 Symptomatic and supportive care: Mainstay
 Extracorporeal: Hyperammonemia, hypernatremia, hypocalcemia, metabolic acidosis

Ethosuximide

MOA: CCB, inhibits low voltage activated T type Ca²⁺ channels

Indication: absence seizure (first line agent)

Long half life, taken once daily qhs

Formulations: capsule, oral solution

not a controlled substance

Side effects: N/V, HA, anorexia, lethargy, sedation, unsteadiness, urticaria, pruritus, hiccups

Serious ADRs: **Neutropenia, SLE (Systemic Lupus Erythematosus), SJS, suicidal ideation**

Ethosuximide (cont)

Drug Interactions: Substrate for CYP3A4, can reduce VPA levels (reason unknown), very few other drug interactions.

Barbiturates (Phenobarbital and Primidone)

MOA: GABA receptor agonist, opens Cl⁻ channels, can block AMPA receptors as well. Long half life, preferably taken once daily qhs. Primidone is metabolized to phenobarbital and acts more on Na⁺ channels than phenobarbital.

Indications: generalized tonic-clonic (not first line), simple or complex with or without secondary generalization (not first line), refractory status epilepticus

Formulations: elixir, oral solution, injection, tablet

Schedule IV controlled substance

Side effects: **SEDATION**, rashes, N/V, sedative/hypnotic effects

Serious ADRs: SJS/TEN, respiratory depression, **narrow therapeutic window**, serum concentrations need to be 15-40 mcg/mL, drug accumulates in renal impairment

Barbiturates (Phenobarbital and Primidone) (cont)

Drug Interactions: **POTENT CYP INDUCER**, also a substrate and inducer for PgP pump. Reduces efficacy of oral contraceptives, including progestin only and etonogestrel implant (Nexplanon)

Special Notes: usually D/C due to ADRs so not a first line option, long term use leads to **dependence with withdrawal** leads to more seizures. May **WORSEN** infantile spasms and absence seizures.

It is the oldest anti-epileptic but no longer used.

Pregabalin (Lyrica)

MOA: same as gabapentin, **Ca²⁺ channel alpha2delta subunit** (even though structure is similar to GABA, doesn't bind to GABA receptors)

Indications: adjunct for focal onset (immediate release only) also more for neuropathy

Formulations: capsule (IR only for seizure)

Schedule V Controlled Substance

Side Effects: sedation, increased BP, dizziness, confusion, rash, nystagmus

Drug Interactions: none significant

Pregabalin (Lyrica) (cont)

Special Notes: additional indication for neuralgia and neuropathic pain

Felbamate

MOA: AMPA receptor antagonist, although there is strong evidence that it can also block NMDA receptors. GABA potentiation.

Indications: focal seizures, and Lennox-Gastaut syndrome (**never first line**)

Formulations: tablet and suspension

Not a controlled substance

Side Effects: N/V, HA, dizziness, **hepatotoxicity**, anorexia

Serious ADRs: **Aplastic anemia (wipe out of bone marrow), Hepatic failure ONLY USE IF NO OTHER OPTION**

Drug Interactions: Inhibits CYP2C19, reduces efficacy of oral contraceptives

Special Notes: **REQUIRES INFORMED CONSENT COMPLETED AND SIGNED**

Status Epilepticus

Definition: Occurrence of two or more convulsions without recovery of consciousness between attacks.

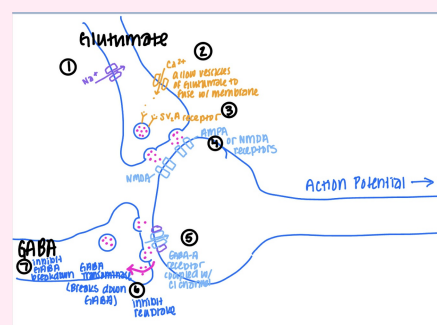
A fixed and enduring epileptic condition (for 30 min or more)

Treatment: Initial treatment with IV Lorazepam (Benzo) 4mg or midazolam is usually helpful regardless of the type of status epilepticus.

Status Epilepticus (cont)

Then if needed phenytoin, then carbamazepine, and other drugs may also be needed to obtain and maintain control in complex partial status epilepticus.

Targets of Anti-Seizure Meds



Targets of Anti-Seizure Drugs

- 1 Na⁺ channels
- 2 Ca²⁺ channels (what allows the vesicles of glutamate to fuse with the membrane)
- 3 sv2A receptor on the glutamate filled vesicles.
- 4 AMPA or NMDA receptors
- 5 GABA-A receptor coupled with a Cl⁻ channel
- 6 Targets the reuptake of GABA (inhibit the reuptake)
- 7 Targets GABA transaminase that breaks down GABA (inhibit GABA breakdown)

Targets of Therapy

- 1- Na⁺ Channel Blockers many drugs, pick and choose based on tolerance and contra-indications.

Carbamazepine

Oxcarbamazepine

Phenytoin

Fosphenytoin

Targets of Therapy (cont)	
	Lomotrigine
	Topiramate
	Valporate*
	Lacosamide
2. Ca2+ Channel Blockers	Ethosuximide
	Maybe gabapentin, but now used for anxiety and neuropathy.
3. sv2A blockers	Levetiracetam
4. AMPA/NMDA Receptor Blockers	Felbamate-AMPA
	Ketamine- NMDA
5. GABA-A Receptor Agonists	feel good drugs, puts you to sleep
	Benzodiazepines- lorazepam, midazolam, diazepam, clobazam (increase in the frequency of Cl ⁻ ion channel opening)
	Barbiturates- phenobarbital, pentobarbital (increase in the duration of Cl ⁻ channel opening)
	Propofol
	Topiramate (Dual action, also a Na ⁺ channel blocker)
6. GABA reuptake inhibitors	Tiagabine (used in really refractory cases)
7. GABA Transaminase Inhibitors	Valproate
	Vigabatrin

Lacosamide	
MOA:	Na ⁺ Channel blocker
Indications:	monotherapy or adjunct for focal (partial) seizure
Formulations:	tablet, injection, oral solution
Controlled Schedule V drug	
Side Effects:	dizziness, HA, N/V, diplopia, ataxia, blurry vision
Serious side effects:	slowed cardiac conduction, monitor PR interval
Drug Interactions:	substrate for CYP3A4, 2C9, 2C19, but interactions are minimal (not an inducer or inhibitor)
Special Notes:	dose adjust for renal/hepatic impairment, well tolerated

Topiramate	
MOA:	broad spectrum, Na ⁺ channels, GABA receptors, and AMPA glutamate receptors
Indications:	Monotherapy or adjunct in focal onset or generalized tonic-clonic, adjunct for Lennox-Gastaut
Formulations:	ER capsule, sprinkle capsule er and regular, tablet
	Not a controlled drug
Side Effects:	dizziness, sedation, dose related impairment, suicidal thoughts, paresthesia's, weight loss, speech difficulties

Topiramate (cont)	
Serious ADRs:	Kidney stones, metabolic acidosis , decreased sweating/-hyperthermia, increased IOP, encephalopathy (when used with VPA)
Drug Interactions:	inhibits CYP2C19, induces 3A4, substrate of PgP, may increase lithium levels, CYP inducers will decrease topiramate levels, may decrease digoxin levels, may reduce efficacy of estrogen and progestin containing contraceptives.
Special Notes:	Cognitive side effects are a big reason for discontinuation

Levetiracetam (Keppra)	
MOA:	Broad spectrum, SVA2 binding on vesicle to decrease glutamate release
Indications:	focal seizure, generalized: adjunct for juvenile myoclonic epilepsy, adjunct for primary tonic-clonic
Formulations:	tablet, oral solution, IV, ER tablet, disintegrating tablet
	Not a controlled substance.
Side Effects:	HA, somnolence, N/V
Drug Interactions:	not metabolized in the liver, so limited drug interactions.
Special Notes:	favorable ADR profile, lack of drug interactions almost complete oral absorption



Benzodiazepines

MOA: **GABA receptor agonist** clobazam is slightly different structurally from other benzos but acts similarly

Indications: adjunct generalized tonic-clonic (clobazam), absence (clobazam, clonazepam-not first line), myoclonic (clobazam-not first line), Status Epilepticus (IV diazepam, midazolam, lorazepam) acute repeated or prolonged seizure in outpatient setting (diazepam rectal gel), atonic/akinetic (clonazepam), adjunct for simple or complex partial (clobazam, clonazepam) adjunct Lennox Gastaut (clobazam)

Formulations: Clobazam (onfi tablet/oral film "- Sympazan"/suspension), Lorazepam ("ativan" injection), Clonazepam ("Klonopin" tablet), Diazepam ("Diastat" rectal gel/injection), clonazepam ("Tranzene" tablet), midazolam (injection/nasal spray)

Schedule IV Controlled Substances

Side Effects: Hypotension and respiratory arrest with IV use, sedation, slowed breathing.

Serious ADRs: Clobazam can lead to SJS and TEN

Benzodiazepines (cont)

Special Notes: Clobazam, clonazepam, and clonazepam: check blood counts and LFTs periodically

Among the most sedating of antiepileptics- CNS depressants

Drug Interactions: CYP2C19, CYP3A4

Gabapentin

MOA: **Ca²⁺ channels alpha2delta subunit** inhibition AP so explains analgesic, anticonvulsant, and anxiolytic activity. (Even though structurally similar to GABA, doesn't bind to GABA receptors)

Indications: adjunct for focal (partial onset) seizure, more for neuropathy

Formulations: capsule, solution, tablet (medication cannot be crushed)

Controlled substance schedule V in Alabama (abuse potential)

Side Effects: sedation, increased BP, dizziness, confusion, rash, nystagmus

Drug interactions: none significant

Special Notes: requires renal dose adjustments in impairment

Indications

Focal Seizures Carbamazepine
Oxcarbazepine

Levetiracetam

Lamotrigine

Phenobarbital (Neonates)

Generalized Absence Seizures Ethosuximide (Preferred)

Valproate 2nd

Lamotrigine

Generalized Myoclonic Seizures Valproate (BEST)

Levetiracetam/L-amotrigine

Benzos

Generalized Tonic-Clonic Seizures Valproate- very good

Levetiracetam

Lamotrigine

Topiramate

Phenytoin/Fosphenytoin

Phenobarbital-neonates

Teratogens

Valproate-inhibits folic acid- the most teratogen risk

Phenytoin/Fosphenytoin (Fetal hydantoin syndrome)

Carbamazepine (Cleft palate, cleft lip)



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