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 Rolando	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 Interations:	**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 increases 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 PTH 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 PgP 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 adjestments

In stable patients, can draw levels at 3-12 month intervals

Phenytoin kinetic are non liner -> 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

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Take Home Points (cont)

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

Phenytoin levels needs 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 Rolando	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 of sensory.
	With or without loss of consciousness
Generalized	starts in a foci and spreads over the entire cortex.
Epileptic "Spams"	Benign Rolando (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)

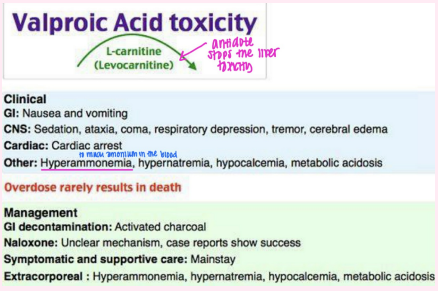
Valproic Acid (Depakene)

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 phenobar and ethosuximide) displaces phenytoin from albumin so increasing free phenytoin levels (toxicity). Increases levels of lamotrigine by inhibiting it's 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



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 substace
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 or 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 **dependance 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 or oral contraceptives
Special Notes:	**REQUIRES INFORMED CONSENT COMPLETED AND SIGNED**

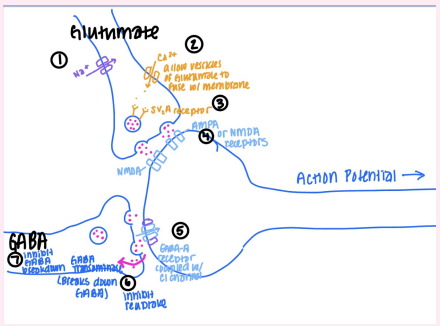
Status Epilepticus

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 contraindications.
	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
Foruml ations:	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
Formul ations:	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, substate 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
Formul ations:	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, clorazepate) adjunct Lennox Gustaut (clobazam)
Formulations:	Clobazam (onfi tablet/oral film "-Sympazan"/suspension), Lorazepam ("ativan" injection), Clonazepam ("Klonopin" tablet), Diazepam ("Diastat" rectal gel/injection), clorazepate ("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 clorazepate: 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
	Oxcarbamazepine
	Levetiracetam
	Lamotrigine
	Phenobarbital (Neonates)
Generalized Absence Seizures	Ethosuximide (Preferred)
	Valproate 2nd
	Lamotrigine
Generalized Myoclonic Seizures	Valproate (BEST)
	Levetiracetam/Lamotrigine
	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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