

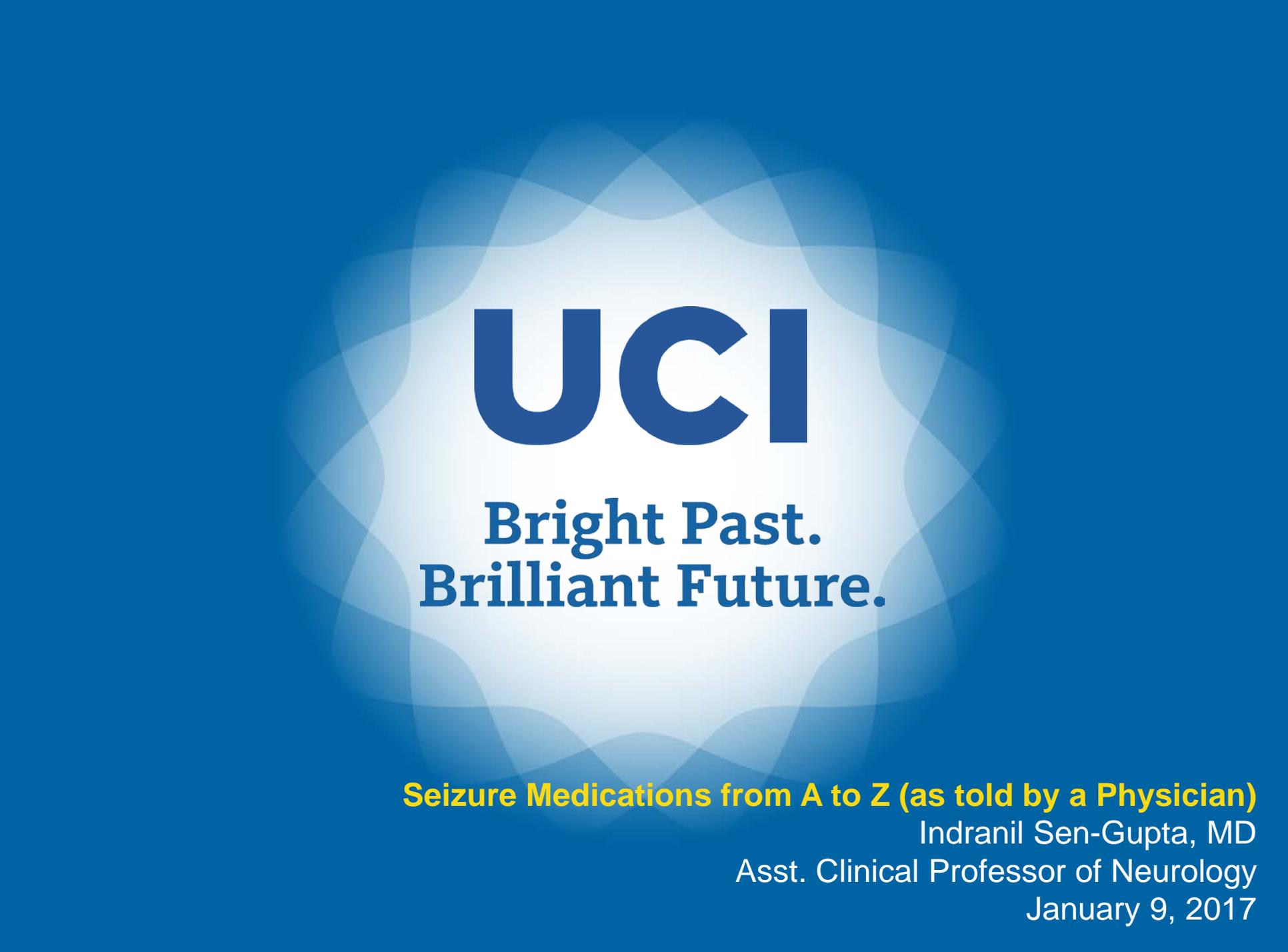


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Seizure Medications From A to Z

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Seizure Medications from A to Z (as told by a Physician)

Indranil Sen-Gupta, MD

Asst. Clinical Professor of Neurology

January 9, 2017

Overview

- To give *general* overview of multiple seizure medications used in outpatient setting
 - Present basic mechanism of action
 - Pearls where given medication could be particularly useful
 - Provide information on side effects and potential cautions

PLEASE NOTE: I will be describing common clinical practice, which may not necessarily match FDA-labeling for a particular seizure medication (possible “off-label.”)

Basic Practice Points/Pearls



- Attempt to use least amount of medication at lowest possible dosages that still provide full seizure control (if possible)
- Optimize dosage of one medication prior to adding a different medication
- Consider whether a medication requires blood levels checked (e.g. especially during pregnancy levels may drop dramatically until delivery)

- Consider impacts on other medications of changing seizure meds with liver-enzyme inducing/inhibiting effects
 - E.g., consider effectiveness of oral contraception, anticoagulation (warfarin) monitoring, effects on other hepatically metabolized seizure meds
- When transitioning one seizure medication to another, add next agent then crosstaper (generally don't abruptly stop one medication when adding the new one)
- Tailor seizure medications to other existing conditions: mood issues, childbearing potential/pregnancy, prior medical conditions, etc.

- If adding additional seizure meds, try to add medication with different mechanism of action from current meds (increase efficacy and possibly minimize side effects)
- Consider if seizure type is focal onset +/- secondary generalization, vs. underlying generalized epilepsy syndrome
 - Some Na-channel blocking agents have theoretical risk of worsening an underlying generalized epilepsy syndrome

HEPATIC ENZYME INDUCERS	
PHENYTOIN	
CARBAMAZEPINE (also autoinduction)	
BARBITURATES	
OXCARBAZEPINE	
TOPIRAMATE (weak)	

MAINLY RENALLY EXCRETED	
GABAPENTIN	
LEVETIRACETAM	
TOPIRAMATE (lesser extend)	

CONCOMITANT MIGRAINE	
VALPROATE	
GABAPENTIN	
TOPIRAMATE	

WEIGHT LOSS	
TOPIRAMATE	
ZONISAMIDE	

PARENTERAL AVAILABLE	
PHENYTOIN/FOSPHENYTOIN	
VALPROATE	
BARBITURATES	
BENZODIAZEPINES	

ONCE DAILY DOSE	
PHENYTOIN	
ZONISAMIDE	
VALPROATE	
PHENOBARBITAL	

HIGH PROTEIN BINDING	
PHENYTOIN	(70-90%)
VALPROATE	(85-95%)
TIAGABINE	(96%)
CARBAMAZEPINE	(75%)
CLOBAMAZEPINE/CLONAZEPAM	(83%-86%)
PHENOBARBITAL	(45%-60%)

ACTIVE METABOLITIES	
CARBAMAZEPINE	EPOXIDE
CLOBAZAM	N-DESMETHYLCLOBAZAM
OXCARBAZEPINE	10-MONOHYDROXY (MHD)
PRIMIDONE	PHENOBARNITAL

AVOID IN YOUNG WOMEN	
VALPROATE	higher teratogenic risk
PHENYTOIN	cosmetic effects, hirsutism

MANAGEMENT OF CLUSTER SEIZURES	
LORAZEPAM PERORALLY	0.03-0.05mg/Kg
RECTAL DIAZEPAM GEL	0.2-0.5mg/Kg

For underlying depression/mood stabilization:

- Lamotrigine, Valproic Acid, Topiramate, Carbamazepine

For pregnancy or childbearing potential:

- Lamotrigine, Carbamazepine, Oxcarbazepine, Levetiracetam
- Consider empiric folate supplementation (~50% US pregnancies unplanned)

Some other “pearls” to note:

- ALL seizure medications have theoretical risk of worsening mood – must counsel on this
- Also, essentially all seizure meds can have cognitive effects (action on whole brain)

- Much of the following referenced from Epilepsy Foundation website, which includes clickable medication list with information (<http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/seizure-and-epilepsy-medicines/seizure-medication-list>)
- Another excellent resource from which several figures referenced (<http://emedicine.medscape.com/article/1187334-overview#a2>)

Brivaracetam

- Briviact

Carbamazepine

- Atretol
- Carbagen SR
- Epitol
- Mazepine
- Tegretol
- Tegrital
- Teril
- Timonil

Carbamazepine-XR

- Carbatrol
- Tegretol XR

Clobazam

- Frisium
- Onfi

Clonazepam

- Epiril
- Klonopin
- Rivotril

Diazepam

- Diastat
- Diazepam
- Valium

Divalproex Sodium

- Depacon
- Depakote
- Epival

Divalproex Sodium-ER

- Depakote ER

Eslicarbazepine Acetate

- Aptiom

Ethosuximide

- Zarontin

Ezogabine

- Potiga

Felbamate

- Felbatol

Gabapentin

- Neurontin

Lacosamide

- Vimpat

Lamotrigine

- Lamictal

Levetiracetam

- Keppra

Levetiracetam XR

- Keppra XR

Lorazepam

- Ativan

Oxcarbazepine

- Oxtellar
- Oxtellar XR
- Trileptal

Perampanel

- Fycompa

Phenobarbital

- Phenobarbital

Phenytoin

- Dilantin
- Epanutin
- Phenytek

Pregabalin

- Lyrica

Primidone

- Mysoline

Rufinamide

- Banzel
- Inovelon

Tiagabine Hydrochloride

- Gabitril

Topiramate

- Topamax

Topiramate XR

- Qudexy XR
- Trokendi XR

Valproic Acid

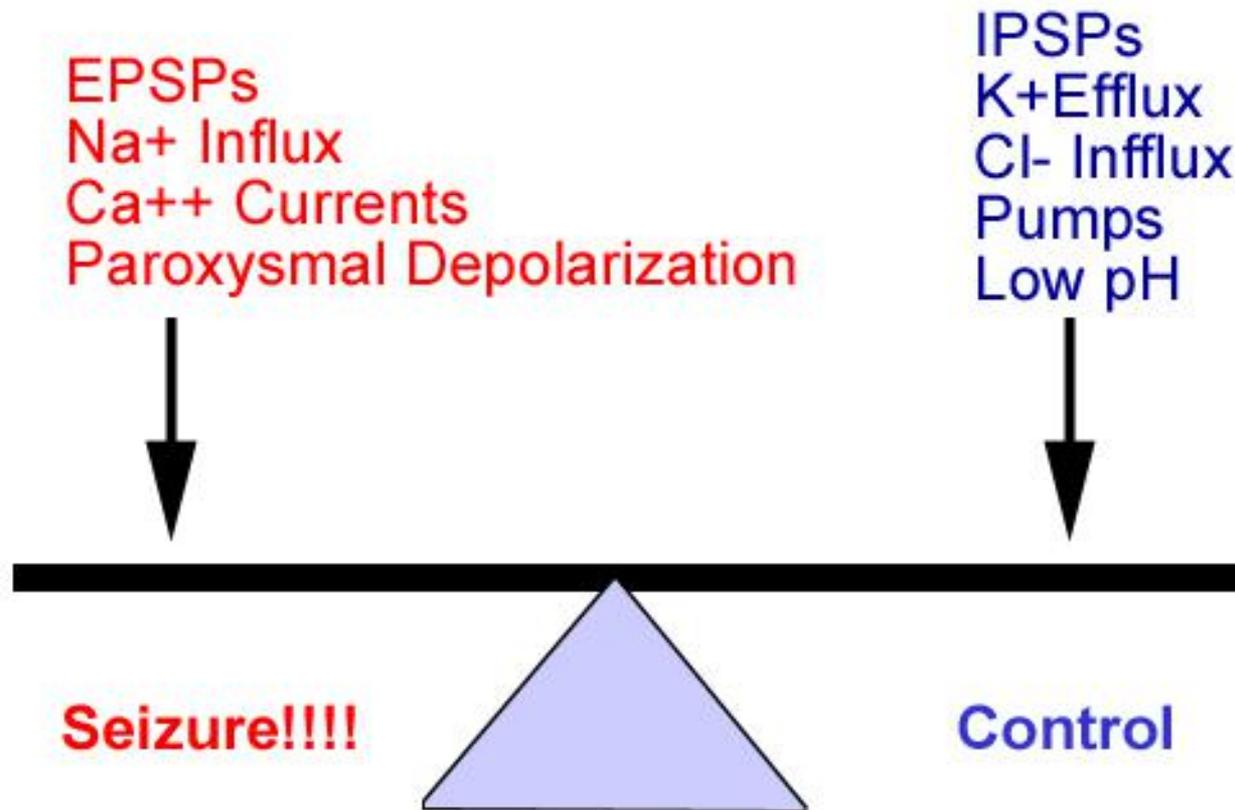
- Convulex
- Depakene
- Depakine
- Orfiril
- Valporal
- Valprosid

Vigabatrin

- Sabril

Zonisamide

- Zonegran



Attempt to Organize by Mechanism...



Some meds have multiple mechanisms...

	Sodium Channel	Calcium Channel	GABAERGIC	Glutamate	CA Inhibitor	Other
Phenytoin →		Ethosuximide	GABA _A Agonist	NMDA receptor	Acetazolamide	Unknown
Carbamazepine →			Benzodiazepines	Felbamate		Levetiracetam
Oxcarbazepine →			Barbiturates	AMPA/Kainate r.		Hormonal
Zonisamide →			Uptake inhibitor	Topiramate		Progesterone
			Tiagabine			
Lamotrigine			GABA-transaminase	Metabotropic		
			Vigabatrine	Experimental		
			GAD modulation			
			Gabapentin			
			Valproate (?)			

Sodium-Channel Blockers

- Most common mechanism of action of seizure meds
- Have highest affinity for Na channel during inactivated state (Na channels cycle open → inactivated → resting with each round of depolarization)
 - Fast inactivation: “ball and chain”
 - Slow inactivation: likely due to rearrangement of channel pore

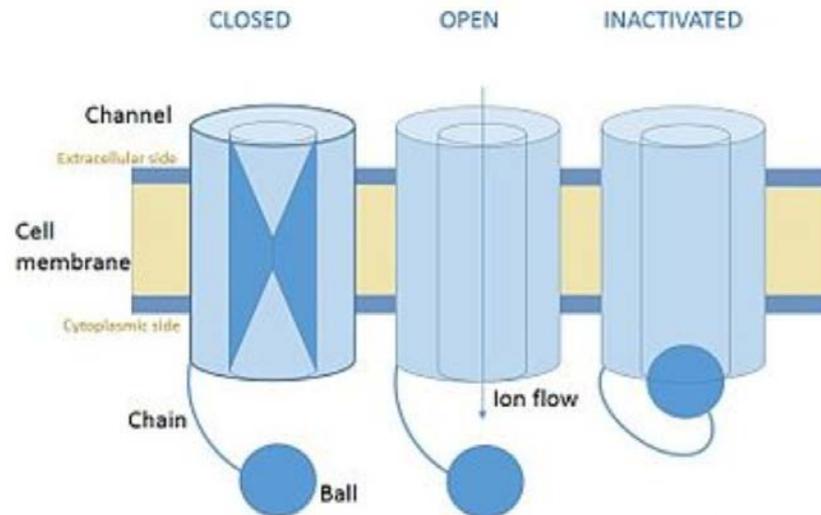
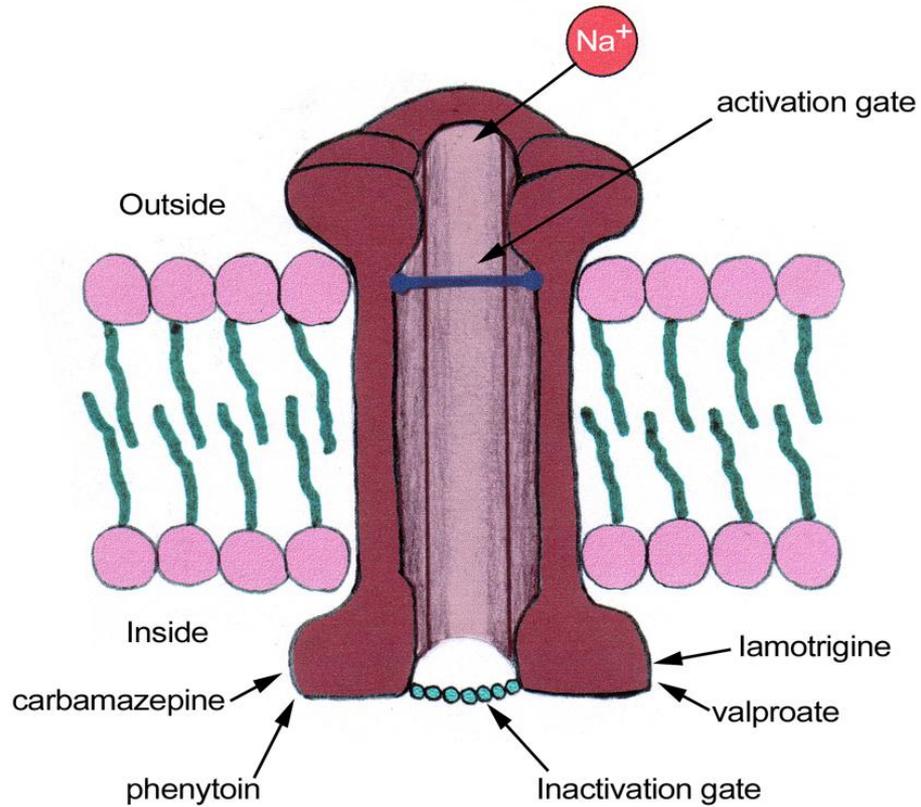


Figure from Wikipedia, “Ball and Chain Inactivation”

- Fast Inactivation Pathway:
 - Carbamazepine, Felbamate, Lamotrigine, Oxcarbazepine, Phenytoin, Rufinamide, Topiramate, Valproic Acid, Zonisamide
- Slow Inactivation Pathway:
 - Lacosamide and Eslicarbazepine selectively enhance this

Enhanced Na⁺ Channel Inactivation



Phenytoin

- An older medicine; can be given IV for loading if needed; use for focal-onset seizures
- Must follow levels, can be influenced by nutrition status, pregnancy, factors affecting liver enzymes (drinking, other meds)
 - Also, follow Vitamin D, liver tests; DEXA bone scan with long-term use
- Cautions: decreased Vitamin D levels, osteoporosis, tremors, gum/teeth issues, neuropathy, elevated liver enzymes (interaction with other hepatically cleared meds), decreased platelets, enhanced metabolism of oral contraception, **fetal effects** (hydantoin syndrome – skull/face abnormalities, underdeveloped nails; cleft lip/palate)

Valproic Acid

- Broader-spectrum seizure agent; can be given IV for loading if needed
 - Other effects for mood stabilization and migraine prophylaxis
- Must follow levels, can be influenced by nutrition status, pregnancy, factors affecting liver enzymes (drinking, other meds)
 - Also, follow Vitamin D, liver tests; DEXA bone scan with long-term use
- Cautions: decreased Vitamin D levels, osteoporosis, tremors, weight gain, irritability, liver enzyme inhibitor (can increase levels of other hepatically cleared meds), decreased platelets, coagulation disorders, fetal effects (neural tube defects)

Examples of Fetal Defects with Seizure Meds

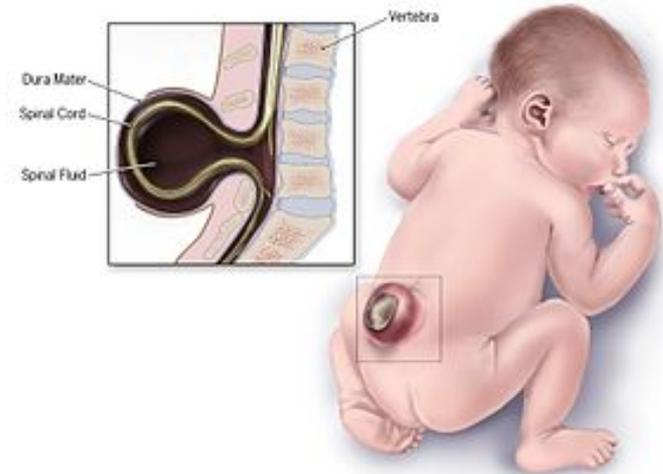
Fetal hydantoin syndrome



Cleft lip and palate



Spina Bifida (Open Defect)



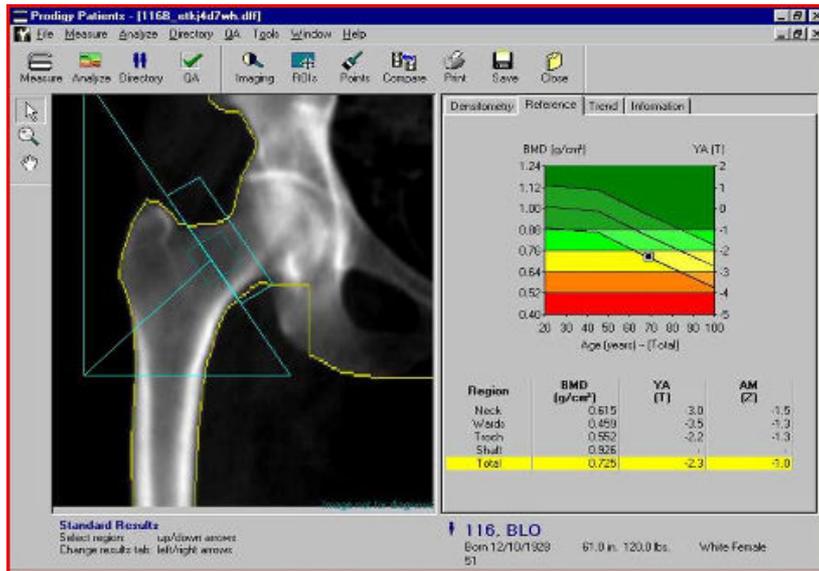
Lamotrigine

- Broad-spectrum seizure agent
- Only available orally
- Follow levels, not set milligram dosing
- Must increase dose gradually over weeks
 - Possibility of Stevens-Johnson rash, which can be life-threatening (if persistent/progressive unexplained rash after starting medication, usually stop the medication)
- Dual uses: mood stabilizer, relative safety in pregnancy (follow levels closely if pregnant)
- Cautions: rash, dizziness, mood changes; oral contraception may decrease Lamotrigine levels (though Lamotrigine has not been shown to affect efficacy of oral contraception)

Carbamazepine and Oxcarbazepine

- For focal-onset seizures; can potentially worsen an underlying generalized epilepsy
- Liver enzyme induction
 - Watch liver functions, be careful about drops in other hepatically processed meds (e.g., warfarin, oral contraception)
 - Keep eye on Vitamin D levels, consider DEXA scan with chronic use
- Follow levels, not based on strict milligram dosing
- Watch Na concentration, as these meds may lower it
- Relative safety in pregnancy (follow levels closely if pregnant)
- HLAB*1502 and risk for Stevens-Johnson rash (in Asian populations – more specifically, Han Chinese)

DEXA Scan



http://whsaz.com/art/DEXA_Femur.jpg
<http://www.body-comp.com/images/dexa.jpg>

Topiramate and Zonisamide

- Broad-spectrum seizure agents
- Topiramate also with actions of augmenting GABA activity, & antagonizing glutamate AMPA receptors
- May have beneficial dual-effects with migraine prophylaxis
- Carbonic anhydrase inhibition
 - Numbness/tingling due to metabolic acidosis, usually transient
- Possibility of kidney stones
 - Encourage good hydration
- Possibility of angle-closure glaucoma
 - Usually seen early if occurs
 - Possibly due to sulfa-allergic response with swelling, congestion, forward rotation of ciliary body
- Other considerations: may cause word-finding issues/cognitive slowing in sensitive individuals; possible decrease of concentrations of combination oral contraception at high dosages

Felbamate

- For focal-onset seizures, and generalized seizures associated with Lennox-Gastaut syndrome
- Multiple possible mechanisms of action: reduction of voltage-dependent Na-channel repetitive firing, enhance GABA-evoked Cl currents, inhibit NMDA-glutamatergic activity
- Requires close monitoring of blood counts and liver functions; possibility of fulminant hepatic failure; insomnia/irritability; complex interactions with other hepatically metabolized seizure meds (requires following levels and possible dose adjustments)
- Powerful medication, usually utilized as a later-line agent due to side effect profile and need for close monitoring

Rufinamide

- For seizures associated with Lennox-Gastaut Syndrome
 - Can be particularly useful for “drop attacks”
 - Seizures resulting in sudden, uncontrollable falls often with injuries
- Complete mechanism of action unknown
 - Effect on voltage-gated Na channels alone doesn't account for unique spectrum of action
- Cautions: may have interactions with other hepatically cleared meds, can have dizziness, drowsiness, headache, nausea, as common side effects

Eslicarbazepine

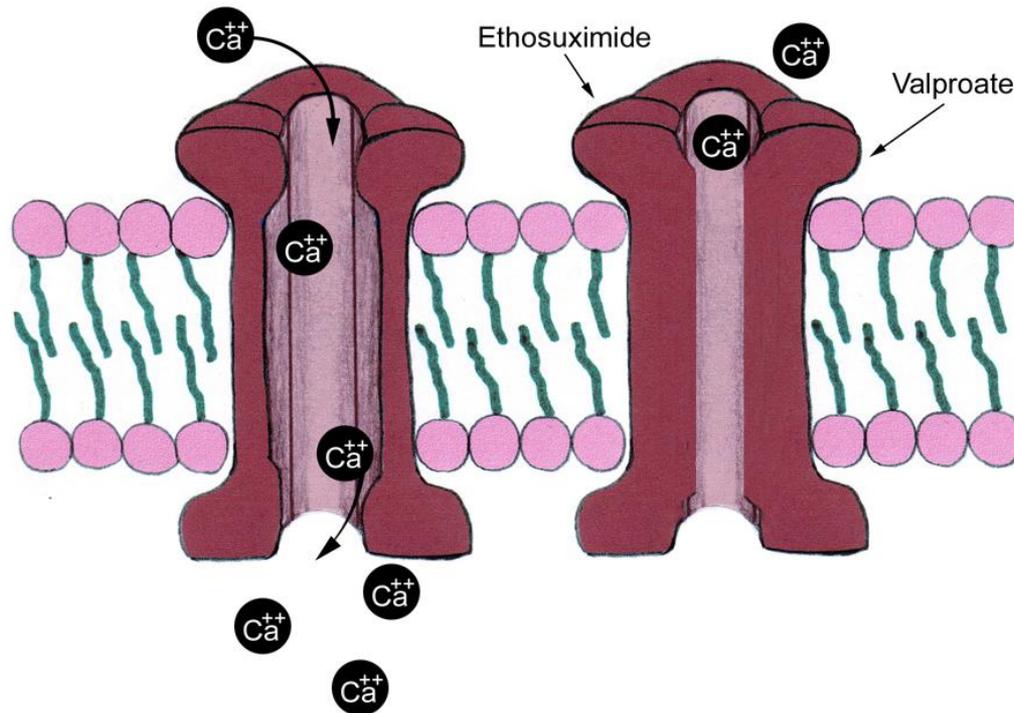
- Newer agent for focal-onset seizures, derivative of carbamazepine and oxcarbazepine
- More selective action on slow inactivation pathway of Na channels
 - May be good adjunct due to synergy
- Fewer interactions than carbamazepine or oxcarbazepine, despite metabolism through liver
 - But, often can use standard daily dosing regimens rather than checking levels
- Similar precautions to carbamazepine & oxcarbazepine, including Na levels & potential for rash in specific populations

Lacosamide

- Newer agent, can be loaded IV, labeled for focal-onset seizures
- More selective action on slow inactivation pathway of Na channels
 - May be good adjunct with other sodium-channel blockers due to synergy
- Minimal interactions, medication levels not routinely checked
- Dosage adjustment in liver impairment

Calcium-Channel Blockers

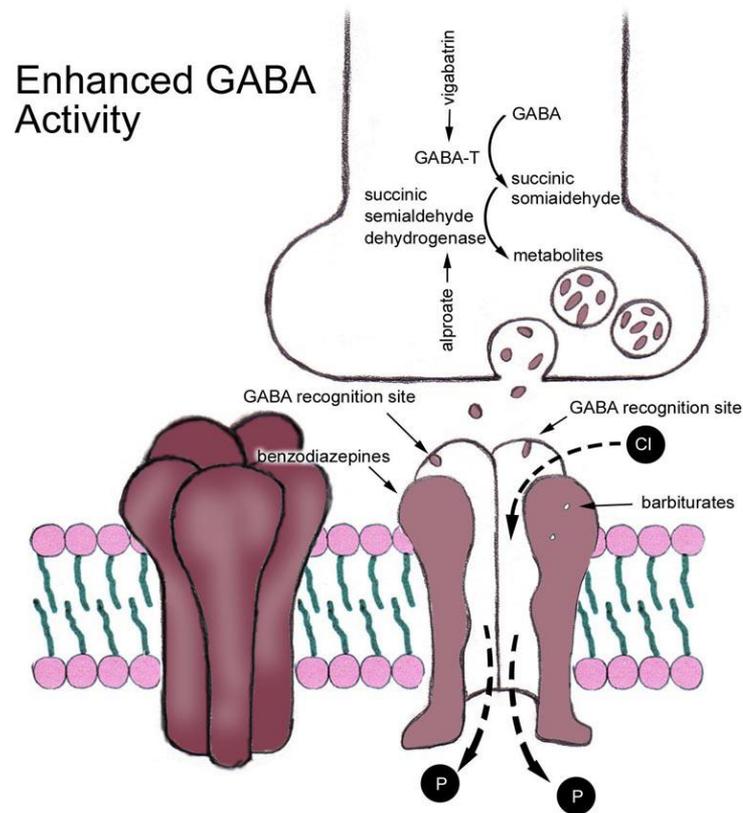
Reduced Current through T-Type Calcium Channels



Calcium-Channel Blockers

- Drugs:
 - Ethosuximide
 - Often drug of choice for childhood absence epilepsy
 - Gabapentin and Pregabalin (Ca-channel $\alpha 2\delta$ ligands)
 - Likely have actions at other channels also, complete mechanisms not completely understood
 - Dual use for neuropathic pain, may have beneficial effects on anxiety
 - Weight gain as one possible side effect of pregabalin

GABA-ergic



GABA-ergic

- GABA agonists
 - Benzodiazepines (↑ frequency of Cl⁻ channel opening)
 - Lorazepam, Clonazepam, Diazepam (rectal available): rapid-onset, often used as-needed for frequent auras/seizure clusters
 - Clobazam, Clorazepate: can be used scheduled as long-term meds, Clobazam can be useful for drop attacks or seizures associated with menstrual cycle
 - Barbiturates (↑ duration of Cl⁻ channel opening)
 - Phenobarbital: older agent, broad-spectrum, induces liver enzymes (e.g., includes enhanced metabolism of oral contraception), other drug-drug interactions

GABA-ergic (cont'd)

- GABA Uptake Inhibitor
 - Tiagabine
- GABA Transaminase Inhibitor
 - Vigabatrin (largely used in children with infantile spasms, can cause peripheral vision loss)
- Cautions: Sedation, possible irritability, can be main side effect of class. Also consider liver function in terms of clearance or interaction with other meds.

SV2A-binding agents

- Drugs: Brivaracetam, Levetiracetam
- Broad-spectrum agents, in practice used for focal or generalized epilepsies
- SV2A important for Ca-dependent neurotransmitter vesicles to release contents
- Advantage is overall lack of drug-drug interactions or enzyme induction/inhibition, rapidity of achieving therapeutic dosing.
- Levetiracetam frequently used as first-line agent.
- Cautions: Underlying mood issues (overall well-tolerated, but may worsen or result in depression/aggression). Brivaracetam newer, and may have less mood effects due to higher affinity for SV2A receptor. May need to adjust Levetiracetam dosage in renal impairment.

Other

- AMPA-blocking: Perampanel
 - Blocks excitatory AMPA glutamate receptors
 - Broad-spectrum agent
 - Potential for mood issues
- Hormonal: Progesterone
 - GABA-ergic
 - For certain instances of seizures worsened in relation to menstrual cycle
 - Can cause bloating, irritability

My Approach

- I look for circumstances where “dual-effects” in addition to seizure control may favor certain agents over others.
- If no such needs:
 - Often I start with levetiracetam for new-onset seizures due to minimal interactions.
 - Then, If needed, lacosamide often a useful second combination agent due to minimal interactions.
- Always consider other medications if above not tolerated; pre-surgical evaluation if ongoing seizures despite 2 meds at therapeutic doses

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Questions + Answers

Seizure Medications From A to Z

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VA Services + Resources

Seizure Medications From A to Z

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Epilepsy Resources

- **VA Epilepsy Centers of Excellence:**
Epilepsy.va.gov
- **VA ECoE Patient Education:**
Epilepsy.va.gov/Patient_Education.asp
- **Epilepsy Foundation of Greater Los Angeles:**
EndEpilepsy.org
- **American Epilepsy Society (AES):**
AesNet.org
- **YouTube: Veterans and Epilepsy educational videos:**
https://www.youtube.com/watch?v=yx45kHDoEgo&list=PL3AQ_JVoBEyzDfAHEptumOPB-PFTH_ya-

VA Contact Numbers

- **24-hour TeleCare Nurse Advice Line:**
 - Veterans registered in VAMCs of West LA, San Diego, Loma Linda, Las Vegas, Long Beach
 - 1-877-252-4866
- **24/7 Veterans Crisis Line - all locations:**
 - 1-800-273-8255, Press 1
- **Pharmacy - Greater Los Angeles VA:**
 - 1-800-952-4852

Veterans Health Administration (VHA) Resources

Resource	What can be found?	Where to find?
Health Care Benefits/ Application Questions	<ul style="list-style-type: none">- Primary care- Mental health care- Preventative care- Specialty care- Inpatient and outpatient pharmacy- Geriatric care- Long term care and support	<ul style="list-style-type: none">▪ Program information: www.va.gov/healthbenefits/▪ 1-877-222-VETS (8387)▪ Eligibility information: www.va.gov/healthbenefits/apply/veterans.asp▪ How to apply: www.1010ez.med.va.gov
Access to Patient Medical Information	My HealthVet – online personal health record system	<ul style="list-style-type: none">▪ www.myhealth.va.gov/index.html▪ 1-877-327-0022
Woman Veteran Support	Women Veterans Health Program	<ul style="list-style-type: none">▪ www.womenshealth.va.gov▪ Call Center: 1-855-VA-WOMEN (829-6636)
Rural Veteran Support	VA Office of Rural Health	<ul style="list-style-type: none">▪ www.ruralhealth.va.gov

Veterans Health Administration (VHA) Resources

Resource	What can be found?	Where to find?
Mental Health Support	<ul style="list-style-type: none">- Information and resources for Veterans and their families- Self-help toolbox- Where to get help- Comprehensive guide to VA Mental Health Services- Veterans Crisis Line website + live chat function	<ul style="list-style-type: none">▪ www.mentalhealth.va.gov▪ http://maketheconnection.net▪ https://www.veteranscrisisline.net/▪ Guide to VA Mental Health Services for Veterans and Families: www.mentalhealth.va.gov/docs/MHG_English.pdf
Veteran Center Information	<ul style="list-style-type: none">- Individual and group counseling- Discharge upgrade information- Community, social service and medical referrals- Employee assistance referrals- VA Benefits assistance referrals	<ul style="list-style-type: none">▪ 1-877-WAR-VETS (927-8387)▪ Locate a Vet Center near you: www.va.gov/directory/guide/vetcenter.asp

Veterans Benefits Administration (VBA) Resources

Resource	What can be found?	Where to find?
Benefits Information & Eligibility Questions	<ul style="list-style-type: none">- Programs, eligibility, online application sites, testimonial videos, eligibility quiz and digital resource links- Hardcopy and online handbook	<ul style="list-style-type: none">▪ www.benefits.va.gov/benefits/▪ 1-800-827-1000▪ http://explore.va.gov▪ www.va.gov/opa/publications/benefits_book.asp▪ www.ebenefits.va.gov
Vocational rehabilitation and Employment (VR&E)	Assistance finding employment with programs	<ul style="list-style-type: none">▪ www.benefits.va.gov/vocrehab▪ http://explore.va.gov/employment-services▪ http://explore.va.gov/
Woman Veteran Support	Women Veterans Health Program	<ul style="list-style-type: none">▪ www.womenshealth.va.gov▪ Call Center: 1-855-VA-WOMEN (829-6636)
Rural Veteran Support	VA Office of Rural Health	<ul style="list-style-type: none">▪ www.ruralhealth.va.gov

Veterans Benefits Administration (VBA) Resources

Resource	What can be found?	Where to find?
Education and Post-9/11 GI Bill Benefits	<ul style="list-style-type: none">- Post-9/11 GI Bill benefits- Eligibility – served at least 90 days on active duty after 9/10/2001	<ul style="list-style-type: none">▪ www.benefits.va.gov/gibill▪ 1-888-GIBILL-1 (442-4551)▪ GI Bill Comparison Tool: https://www.vets.gov/gi-bill-comparison-tool
Pension	Benefits descriptions, eligibility, application forms online	<ul style="list-style-type: none">▪ www.benefits.va.gov/pension
Disability Compensation Questions	<ul style="list-style-type: none">- Disability compensation is a tax-free benefit paid to eligible Veterans- Eligibility determined by injuries/diseases from/aggravated by service	<ul style="list-style-type: none">▪ www.benefits.va.gov/compensation/types-disability.asp
Insurance and TSGI/SGLI Questions	Life Insurance information	<ul style="list-style-type: none">▪ www.benefits.va.gov/insurance▪ 1-800-419-1473



DISCUSSION TIME

Led by

Laurette Hayden, LMFT,
Psychotherapist



THANK YOU!

Join us next month!

February 13, 2017

