2023 GW Epilepsy Board Review & Best Practices

ASMs I: Sodium Channel

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Disclosures

- Disclosure of Financial Relationships
  - None

- Off-Label Usage
  - Use of lacosamide for status epilepticus

ASMs acting on the sodium channel

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Objectives

- Review the mechanism of blocking sodium channels
- Review pharmacokinetics of classical sodium channel blockers PHT, CBZ, OXC, ESL, LTG, LCM, RFM
- Review key interactions of above
- Review main adverse effects of above
- Review clinical use of classical sodium channel blockers

ASM main mechanisms of action

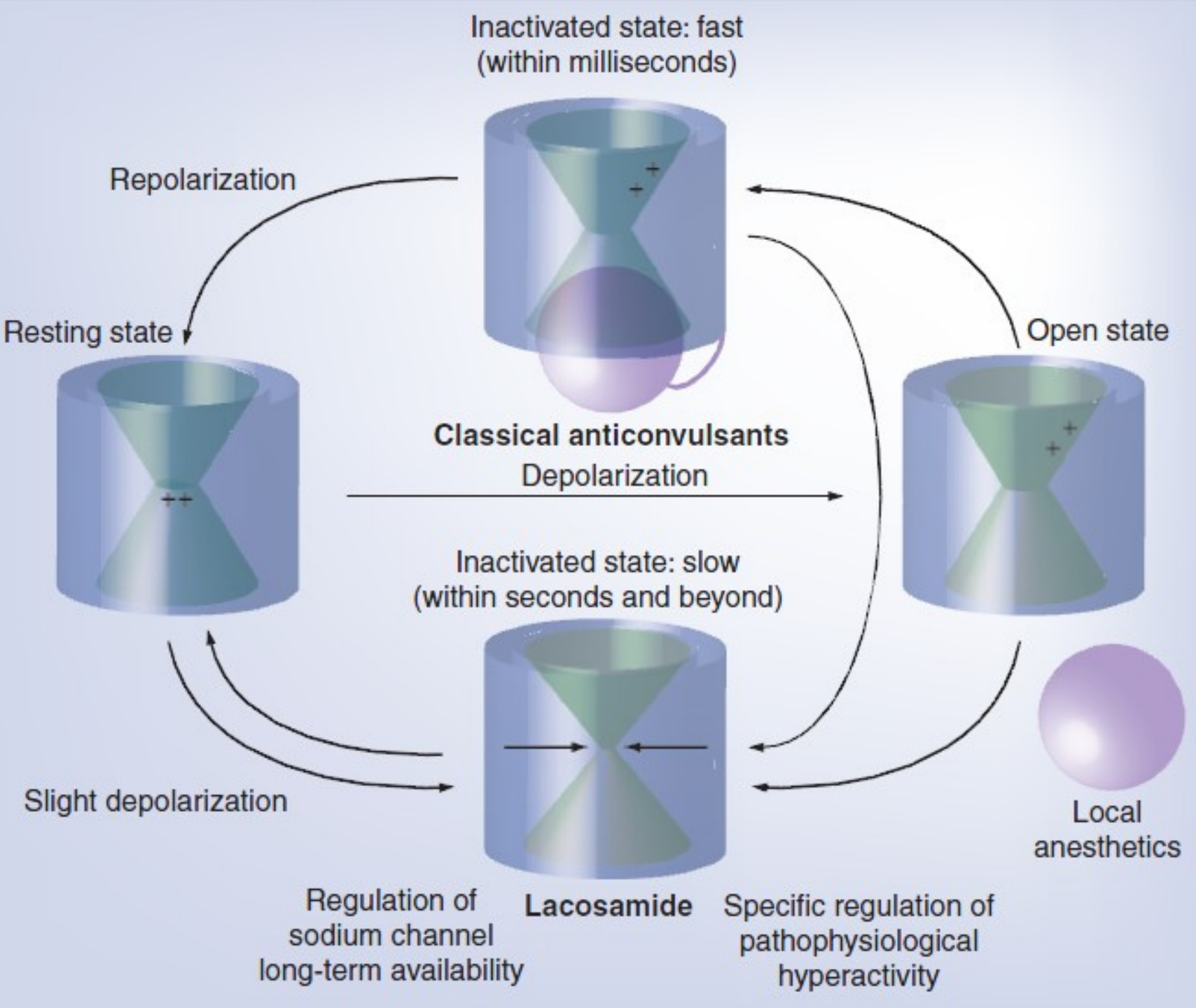
- **Na channel blocking**
- Enhancing GABA
- Glutamate receptor antagonism
- Blocking high voltage activated calcium channels
- Blocking T- calcium channels
- Binding Alpha-2-delta subunit of voltage-activated calcium channels
- Binding synaptic vesicle protein SV2A
- Carbonic anhydrase inhibition
- K-channel opening
- Modulation of intracellular Ca
- Enhancing serotonin

Blocking voltage-gated sodium channels as an ASM mechanism

- Sodium channels open in response to membrane depolarization, allowing positive sodium ions into the neuron, which increases neuronal depolarization and facilitates the spread of action potentials
- After the channel closes, it remains inactive for a certain period - a refractory period- during which membrane depolarization cannot reopen it.
- During seizures, neurons undergo depolarization and fire action potentials at high frequencies. Inhibition of high frequency firing is thought to be mediated by decreasing the ability of sodium channels to recover from inactivation
- Drugs that increase the refractory period decrease the frequency of action potentials

Fast versus slow inactivation of VGSC

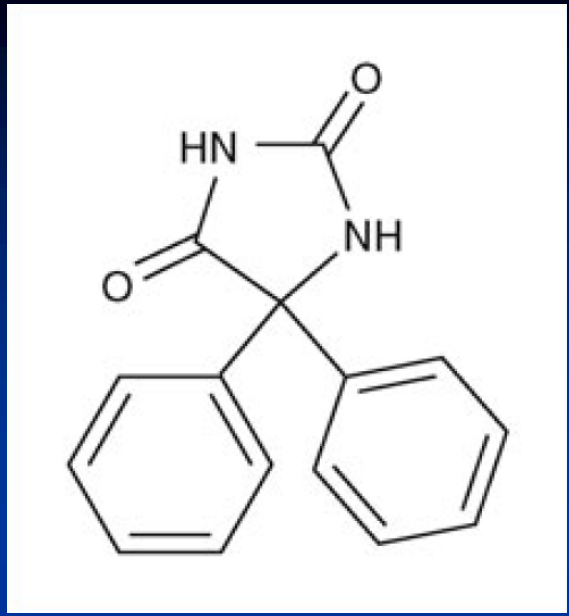
- Fast inactivation occurs on a time scale of milliseconds.
- Slow inactivation occurs over the time course of seconds to minutes.
  - involves modification of the shape of the sodium channel


Inactivated state: fast
(within milliseconds)
Repolarization
Resting state
Open state
Classical anticonvulsants
Depolarization
Inactivated state: slow
(within seconds and beyond)
Slight depolarization
Local
anesthetics
Regulation of
sodium channel
long-term availability
Lacosamide
Specific regulation of
pathophysiological
hyperactivity

ASMs and Na channel blocking

- Enhancement of fast inactivated state- blocking of sustained repetitive firing:
  - Phenytoin, carbamazepine, oxcarbazepine, lamotrigine, rufinamide, eslicarbazepine
- Selective enhancement of slow inactivation of voltage-gated sodium channels
  - Lacosamide
- Multiple mechanisms, including effect on sodium channels
  - Valproate, felbamate, topiramate, zonisamide, cenobamate

Phenytoin (PHT)



- In use since 1938 when Houston and Merritt discovered its efficacy in the MES model
- MOA: binds to the active state of the sodium channel, slows recovery rate of inactivated channel, and reduces high frequency firing (as might occur during a seizure) while allowing normal action potentials to occur.
- Available as oral preparations and parenteral solution

PHT- Absorption, distribution

- **Rate and extent of absorption may differ among different formulations and is affected by many factors, including age and food** (decreased in neonates, with NG feedings, calcium, antacids).
- Limited absorption in the stomach. **Absorption primarily in the duodenum**, where the higher pH increases PHT solubility.
- Tmax 4-8 hours (up to 12 hours), sooner with immediate release
- V_d= 0.78 L/Kg
- **Protein binding: ~90%**

PHT- Metabolism

- **Major pathway of elimination is hydroxylation, mediated mainly by the cytochrome P450 enzyme CYP2C9> CYP2C19.**
- **Nonlinear kinetics**- small changes in CYP2C9 activity may have clinically significant effects. Some alleles are associated with reduced clearance.
- Importance of CYP2C19 increases with higher levels. Some alleles and inhibitors (e.g. ticlopidine or isoniazid) may lead to accumulation

PHT- Elimination

- PHT follows nonlinear elimination kinetics, unlike other ASMs
- **$T_{1/2}$ is dependent on serum concentration**. Initial $T_{1/2}$ = ~ 22 h (range 8–60).
- The half-life will increase as the serum concentration increases within and above the recommended therapeutic range (10-20 mg/L).
- ~95% is excreted in urine and feces as metabolites, ≤ 5% unchanged PHT

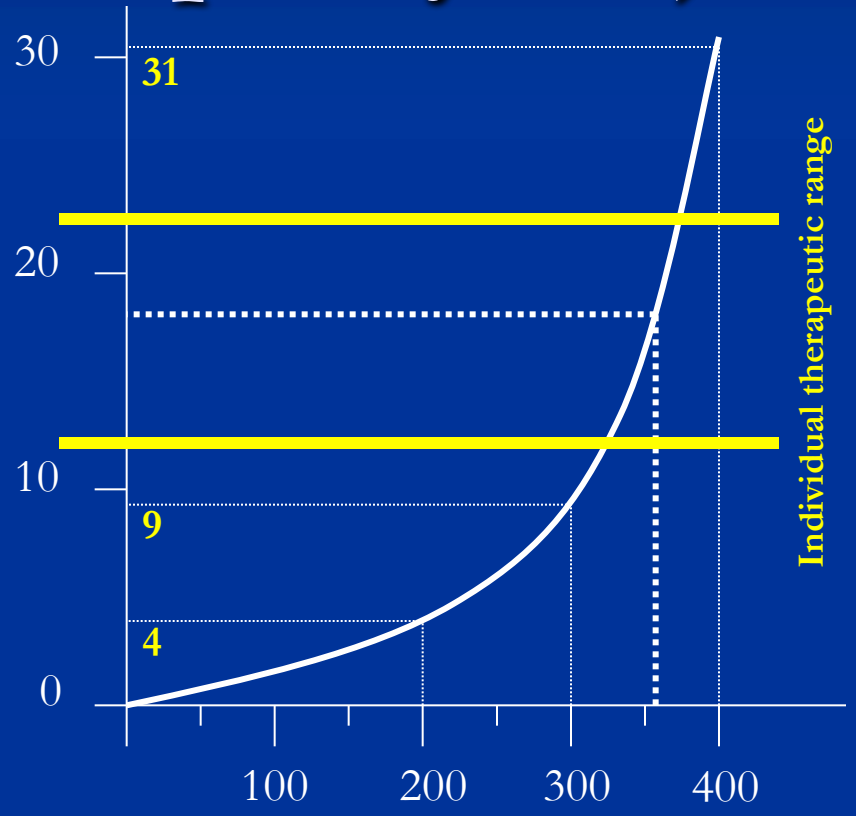
PHT- Nonlinear elimination kinetics

- Enzymes responsible for most of PHT elimination are partially saturated at concentrations within the recommended therapeutic range (with individual variation as to concentration at which this phenomenon starts).
- These enzymes are not able to increase their activity in proportion to PHT concentration as the concentration increases to the recommended therapeutic range.
- Steady-state PHT level increases disproportionately as the maintenance dose is increased within and above the recommended therapeutic range.

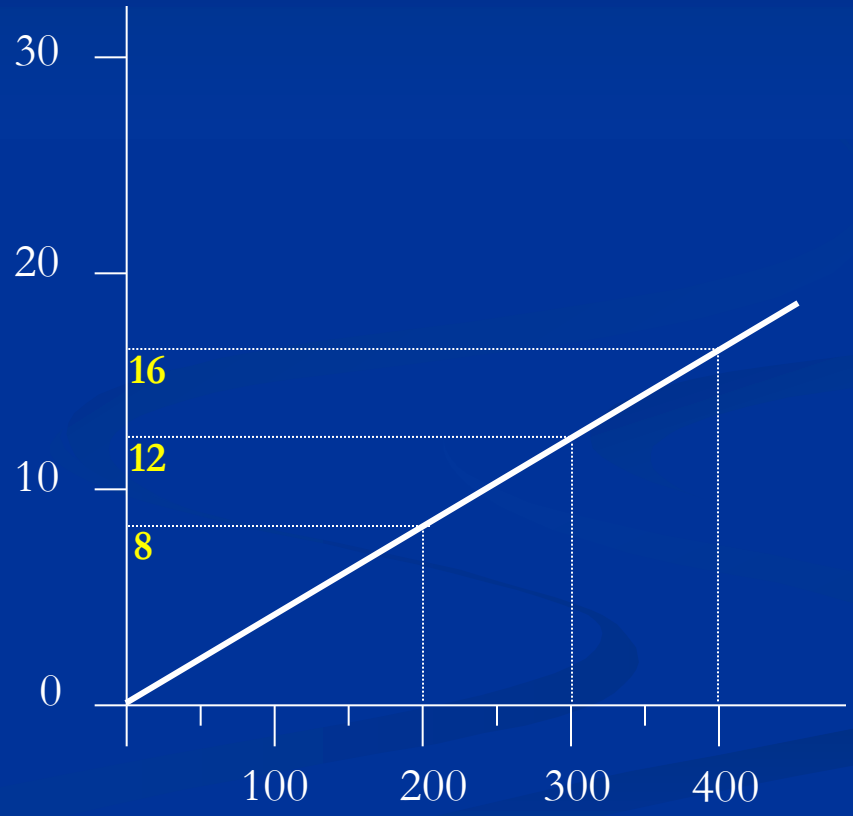
Phenytoin nonlinear kinetics- Example of consequences

- Example 1: a daily dose of 300 mg per day results in a serum concentration of 9 mg/L. Increasing the dose to 400 mg per day (1/3 increase) would have increased the steady state concentration by 1/3 to 12 mg/L if phenytoin were to follow linear elimination kinetics. With its nonlinear kinetics, the concentration may increase disproportionately to 31 mg/L with associated toxicity
- Example 2: a patient presents with phenytoin toxicity and a serum concentration of 40 mg/L. The $T_{1/2}$ was previously estimated at 24 hours. However, after phenytoin was stopped it took 3 days for the serum concentration to go below 20 mg/L

Non-linear kinetics (ex: phenytoin)



Linear kinetics (other ASMs)



PHT- Formulations

- Extended release capsules contain phenytoin sodium
- Immediate release tablets contain phenytoin, so they are not exactly equivalent.

PHT- Interactions

- **PHT affected by drugs that**
  - **Decrease absorption (e.g. NG tube feedings)**
  - **Compete for protein binding (VPA)**
  - **Enzyme inducers or inhibitors**
- PHT is **a potent enzyme inducer** that reduces the efficacy of other ASMs metabolized by p450 enzyme system

Select drugs that reduce PHT clearance

- Acute alcohol intake
- Amiodarone
- Azoles (fluconazole, ketoconazole, etc…)
- H2- antagonists (e.g. cimetidine)
- Several ASMs (ethosuximide, methsuximide, felbamate, oxcarbazepine, topiramate, cenobamate)
- Fluoxetine, fluvoxamine
- Isoniazid
- Others

PHT- Protein binding

- PHT is ~90% protein bound, 10% free
- Free level is responsible for therapeutic effect and for toxicity
- Free fraction increases in presence of low protein state, renal failure, hepatic failure, old age, or with co-administration of VPA.

PHT- Adverse effects

- Concentration-dependent AEs: nystagmus, ataxia, incoordination, diplopia, dysarthria, drowsiness.
- **Exacerbation of seizures may occur with levels > 30 mcg/ml**
- Some may experience prominent AEs within the recommended therapeutic range, including cognitive AEs.

PHT- Idiosyncratic AEs

- Idiosyncratic reactions may be related to formation of an arene oxide, a reactive metabolite that forms due to inadequate epoxide hydrolase activity.
- Allergic rash occurs in up to 8.5% of patients
  - Stevens Johnson syndrome, toxic epidermal necrolysis less common
- 'Hypersensitivity syndrome" with rash, fever, lymphadenopathy, eosinophilia, elevated liver enzymes, renal failure, is very uncommon.

PHT- Long-term AEs

- Gingival hyperplasia, hirsutism, acne
- Cerebellar atrophy (may also occur after acute high dose)
- Reduced bone density
- Reduced folate levels, anemia, macrocytosis
- Teratogenicity

AEs- IV solution

- **Local reactions**
  - Pain and burning at infusion site
  - Phlebitis
  - Cellulitis or necrosis from extravasation
  - Purple glove syndrome with discoloration then petechial rash
- Cardiovascular AEs related in part to vehicle (propylene glycol), can be avoided with slowing of infusion rate (max 50 mg/min)
  - hypotension, conduction abnormality, arrhythmia

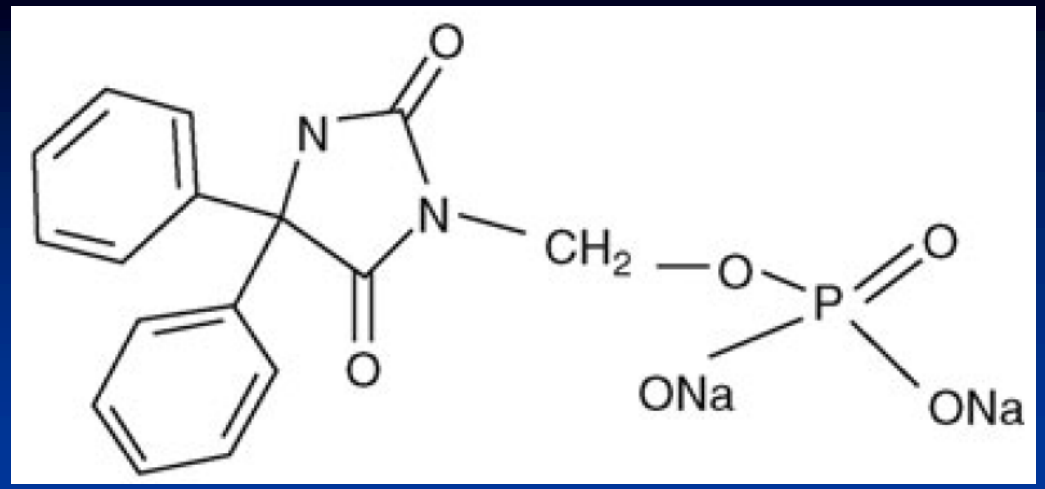
PHT- Efficacy and Clinical Indications

- Effective against focal (partial) onset seizures and generalized tonic-clonic seizures. Efficacy against tonic and atonic seizures less well established.
- **Not effective against generalized myoclonic or absence seizures** (and may exacerbate them).
- The most frequently used ASM for many years, but its use has declined considerably since the appearance of newer-generation ASMs with improved tolerability.

PHT- Acute loading

- Oral loading dose can be given (18 mg/Kg divided into three doses given 2 to 3 hours apart).
- IV loading dose for status epilepticus is 18-20 mg/Kg. Phenytoin should be diluted in normal saline, not dextrose 5% in water; max rate 50 mg per minute into a large vein. ECG and BP monitoring recommended.
- **Intramuscular injection not recommended due to slow and erratic absorption, and crystallization at injection site causing pain.**

Fosphenytoin



- Phenytoin pro-drug
- Can be given IV or IM
- Rapidly and completely converted to phenytoin (by cleavage of the phosphate group by nonspecific phosphatases). Conversion $T_{1/2}$ is ~8-18 minutes. Conversion is complete in a little more than 1 hr.
- Highly bound to serum albumin (95% to 99%)- displaces phenytoin from protein binding sites after IV administration, increasing unbound phenytoin concentrations as a function of fosphenytoin concentration.

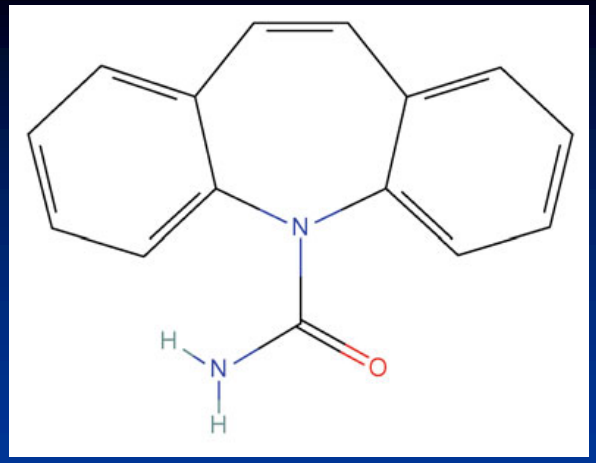
Fosphenytoin indications/dosing

- Indicated for replacement of oral PHT or for IV or **IM loading**
- Marketed in phenytoin equivalents (PE), so loading dose is equivalent to phenytoin loading dose. Loading dose 18-20 mg PE/Kg, max rate 150 mg PE/min
- Therapeutic PHT level usually reached within 10 min after IV loading, within 30 min after IM administration.

Fosphenytoin AEs

- Lower incidence of local reactions.
- IV administration commonly associated with **paresthesias/ itching**, most often in the groin/ perianal region, on the trunk, or the back of the head; this is related to infusion rate and subsides rapidly after the end of infusion. It is not seen with IM administration.

Carbamazepine (CBZ)



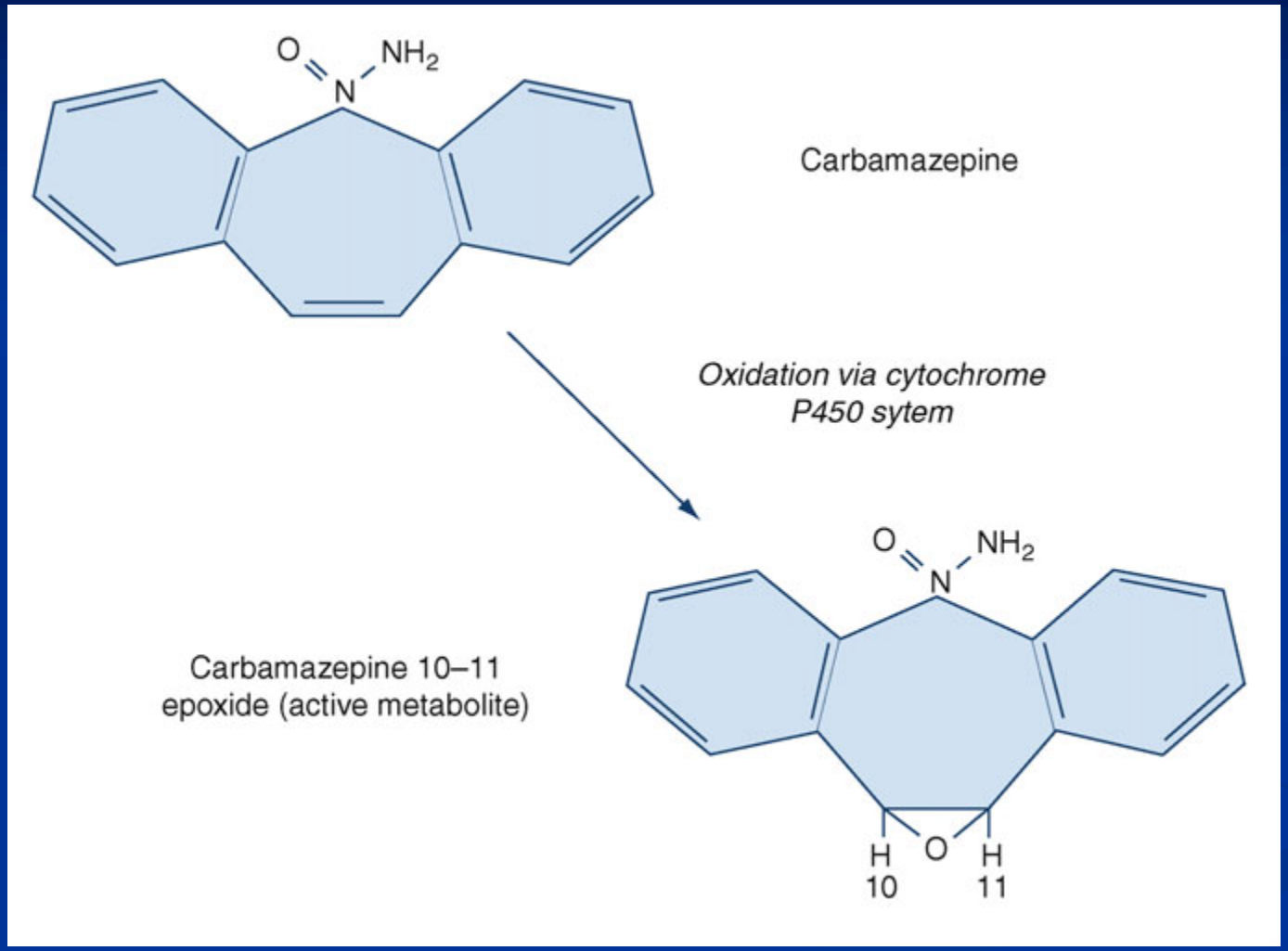
- Similar in structure to tricyclic antidepressants.
- MOA: reduces high frequency neuronal firing through action on the sodium channel, in both a voltage- and use-dependent fashion

CBZ- Absorption, distribution

- Bioavailability ~ 80-90%
- T max = 3-4 hours.
- Lipophilic- crosses the blood-brain barrier readily
- Poorly water soluble; IV preparation approved in 2016 for short-term replacement therapy
- V_d= 0.8-2 L/Kg
- **Protein binding: 75%**

CBZ- Metabolism, elimination

- **Cleared almost entirely via hepatic metabolism.**
- Major pathways are epoxide-diol pathway, aromatic hydroxylation, and conjugation.
- **Most important product is CBZ-10,11-epoxide** (via oxidation through CYP3A4 and CYP2C8). It is active and also responsible for some adverse effects.
- **Induces its own metabolism (autoinduction)**, with increasing clearance, shortening of $T_{1/2}$ and lowering of serum concentration over time (process takes 2-4 weeks). Cannot be started on target maintenance dose.
- $T_{1/2}$= 12-17 h after autoinduction is complete


O
NH2
N
Carbamazepine
Oxidation via cytochrome
P450 sytem
Carbamazepine 10–11
epoxide (active metabolite)
O
NH2
N
H
10
O
H
11

CBZ- Interactions

- **Potent inducer of p450 enzyme system** (CYP3A4, CYP2C9, CYP2C19, and CYP1A2), increasing clearance of agents metabolized by these enzymes
  - Hormonal contraceptives
  - Warfarin
  - Simvastatin
  - Valproate, lamotrigine, etc..

CBZ- Interactions

- **Affected by agents that induce or inhibit CYP3A4 isoenzymes**
  - **Inhibitors include erythromycin and related antibiotics (not azithromycin), fluoxetine, propoxyphene, verapamil, diltiazem, grapefruit juice,** etc…
- CBZ-epoxide increased by concomitant use of valproate, felbamate, oxcarbazepine, zonisamide

CBZ- Adverse effects

- Most common AEs are nausea, GI discomfort, headache, dizziness, incoordination, unsteadiness, vertigo, sedation, tiredness, blurred vision, diplopia, nystagmus, tremor.
- Leukopenia is common (10-20%)- most often transient but may be persistent.
- Hyponatremia
- Cognitive impairment on neuropsychological testing
- Weight gain
- Decreased bone density
- Increased sex hormone binding globulin and decreased testosterone

CBZ- Idiosyncratic AEs

- Rash
- Stevens-Johnson syndrome, and toxic epidermal necrolysis are rare.
- Rare hypersensitivity syndrome, with fever, rash, and organ involvement.
- SLE rare
- Hepatotoxicity rare
- Aplastic anemia rare (1 per 200,000)

CBZ- Idiosyncratic AEs

- **Strong association between the HLA-B*1502 allele and CBZ-induced Stevens- Johnson syndrome in Asian populations** and individuals of Asian descent
- FDA issued an alert and updated product labeling recommending genetic testing of HLA-B polymorphisms to predict carbamazepine-induced serious skin reactions in individuals of Asian descent.

CBZ- Efficacy and indications

- Effective against focal (partial) onset seizures and against generalized tonic-clonic seizures
- **May exacerbate absence and myoclonic seizures** as well as atonic seizures.
- Recommended therapeutic range 4-12 mg/L

CBZ- Place in therapy

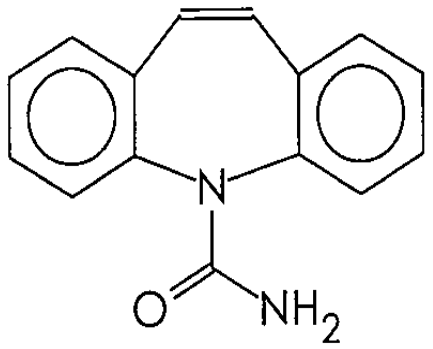
- Had the best balance of efficacy and tolerability in the large cooperative VA study. As a result, it became the standard treatment for focal seizures.
- No drug has been demonstrated to be more effective than CBZ, but its use has declined with the marketing of new ASMs with pharmacokinetic advantages.
- LTG, OXC, GBP had better tolerability than immediate release CBZ. However, **comparative trials using extended release CBZ have failed to show superior tolerability of LTG, LEV, ZNS, ESL or LCM**.
- Nevertheless, enzyme induction and pharmacokinetic interactions have been issues favoring newer ASMs. On the other hand, economic considerations favor the less-expensive CBZ.

Comparison of CBZ, PHB, PHT, or PMD in partial and secondarily generalized tonic-clonic seizures Mattson et al, N Engl J Med. 1985

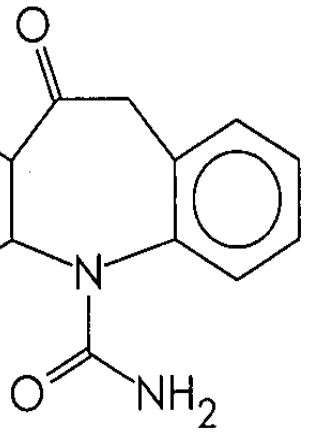
- 10-center, double-blind trial to compare efficacy and toxicity of carbamazepine (CBZ), phenobarbital (PHB), phenytoin (PHT), primidone (PMD) in partial and secondarily generalized tonic-clonic seizures (SGTCS)
- 622 adult patients were randomly assigned to CBZ, PHB, PHT, or PMD and were followed for two years or until the drug failed due to uncontrolled seizures or unacceptable side effects
- **Overall treatment success was highest with CBZ or PHT, intermediate with PhB, and lowest with PMD** ($p<0.002$). **PMD caused more intolerable acute toxic effects** (nausea, vomiting, dizziness, sedation, decreased libido, impotence)
- **Control of SGTCS did not differ significantly with the four drugs.**
- **CBZ provided complete control of partial seizures more often than PMD or PhB** ($p<0.03$).
- "Overall, CBZ and PHT are recommended drugs of first choice for single-drug therapy of adults with partial +/- SGTCS."

Oxcarbazepine (OXC)

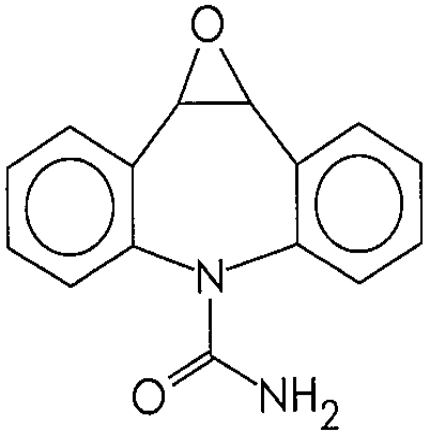
- Structurally related to CBZ, but different from CBZ in metabolism and induction of metabolic pathways- rapidly and extensively metabolized to an active monohydroxy derivative (MHD)- no epoxide formation
- MOA similar to CBZ



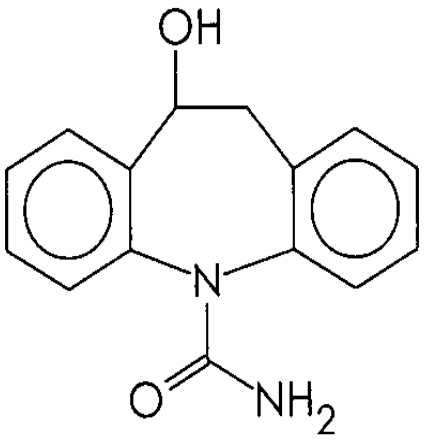
Carbamazepine



Oxcarbazepine



10,11 - epoxycarbamazepine



10-hydroxycarbazepine

OXC- Absorption, distribution

- Oral absorption is virtually complete (bioavailability ~99%)
- MHD Tmax 4-6 hours after OXC dose (OXC Tmax 1-3 hours)- 7 hrs after extended release
- MHD V_d= 0.7-0.8 L/Kg
- **MHD Protein binding: 40%** (OXC 60%)

OXC- Metabolism, elimination

- OXC **rapidly converted to the active metabolite monohydroxyderivative (MHD)**, which is then further metabolized
- MHD T½= 8-10 hrs (OXC T½= 1 to 3.7 hrs)
- **Does not induce its own metabolism**

OXC- Interactions

- MHD level decreases with enzyme inducing ASMs (EIASMs)
- **Does not induce metabolism of other ASMs or warfarin**
- **Weakly induces CYP3A4 responsible for estrogen metabolism**
- **Weakly inhibits CYP2C19, raising PHT level at high doses**
- **Is not affected by erythromycin, fluoxetine, propoxyphene, grapefruit juice,** etc..

OXC- Adverse effects

- Most common are somnolence, headache, dizziness, blurred vision, diplopia, fatigue, nausea, vomiting, ataxia
- **Hyponatremia- more likely in older age or in association with diuretic intake**
- Rash- ~2-4%
- Does not have CBZ effect on SHBG and testosterone

OXC- Efficacy and clinical indications

- Effective against **focal-onset seizures**
  - FDA- mono or adjunctive Rx- adjunctive in children 2-4 years
- **Multiple comparative monotherapy trials for new onset partial epilepsy**
  - OXC equal in efficacy to PHT and CBZ, but with less adverse effects/ superior tolerability
  - OXC equal in efficacy and tolerability to VPA
- **May exacerbate absence and myoclonic seizures**

OXC- Conversion from CBZ

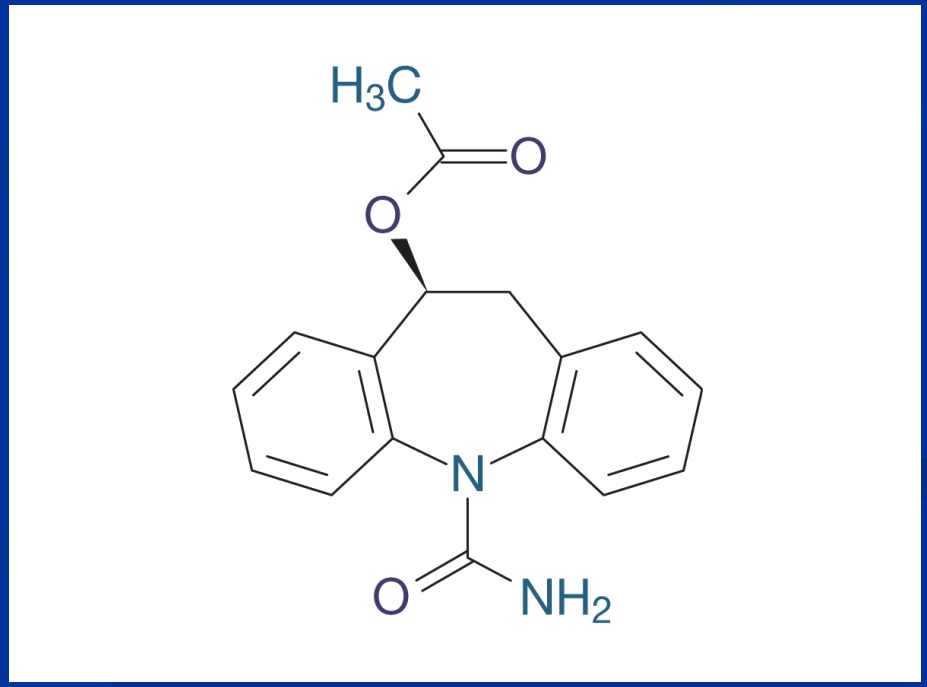
- Conversion from CBZ can be made overnight using a 1.5 to 1 ratio at a CBZ dose of ≤ 800 mg. Lower conversion ratio advisable at higher CBZ doses.
- **Conversion from CBZ to OXC will be accompanied by enzyme de-induction** and decreased clearance of medication metabolized by p450 enzymes.
- **Sodium level may decrease after conversion from CBZ**

Eslicarbazepine Acetate (ESL)

- Approved for marketing in the USA in 2014.
- A prodrug of eslicarbazepine- rapidly converted to the active metabolite (S)-licarbazepine by hydrolytic first-pass metabolism. (S)-licarbazepine is the active enantiomer of the monohydroxy derivative, which is the active metabolite for oxcarbazepine. The monohydroxy derivative from oxcarbazepine is a racemic mixture of the active (S)-licarbazepine and the inactive (R)-licarbazepine.
- Eslicarbazepine acts by blocking sodium channels and stabilizing the inactive state of the voltage gated Na channel.

ESL- Absorption, distribution

- Bioavailability >90%
- T max 1-4 hours post-dose.
- Food has no effect on absorption
- Protein binding <40%
- Vd= 0.87 L/Kg



ESL- Metabolism, elimination

- Eslicarbazepine is metabolized to inactive compounds. It is not subject to autoinduction.
- Renal excretion, 60% unchanged, 30% glucuronide conjugate, 10% other metabolites.
- **$T_{1/2}$ ~ 13-20 hours in plasma, 20–24 hours in CSF**

ESL- Interactions

- **Moderate inhibitory effect on CYP2C19**
  - can cause increased plasma concentration of phenytoin and other drugs metabolized by CYP 2C19
- **Can induce CYP3A4**, decreasing plasma concentrations of estrogen and drugs metabolized by CYP 3A4
- No apparent autoinduction
- Enzyme inducers may reduce level of eslicarbazepine

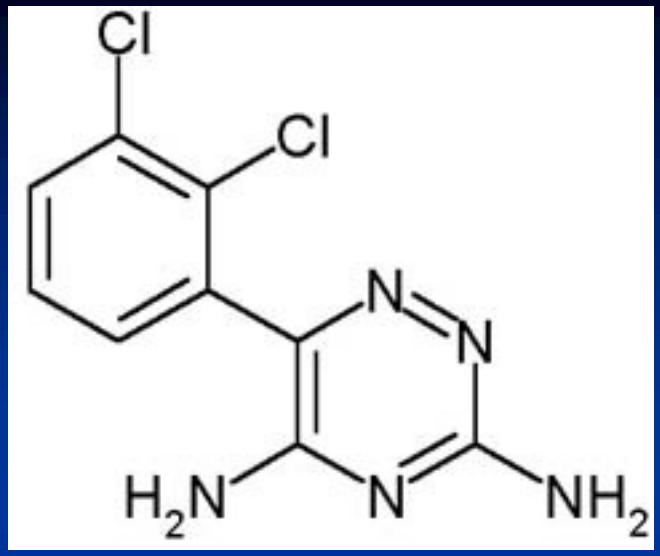
ESL- Adverse effects

- Most common are dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, ataxia, blurred vision, and vertigo
- Hyponatremia (≤ 125 mEq/L) reported in up to 1.5% at 1200 mg per day
- Rash- up to 3% at 1200 mg per day

ESL- Efficacy and clinical indications

- Effective against **focal seizures**
- FDA indication: treatment of partial-onset seizures in patients ≥4 years
- Should be avoided in IGE.
- Theoretical considerations suggest ESL could be considered as first-line monotherapy for focal seizures, with tolerability advantages over immediate-release oxcarbazepine (but financial considerations may be an obstacle).

Lamotrigine (LTG)



- Approved in the USA in 1995, licensed in Europe in 1991
- Mechanism of action: blocking sodium channels; secondarily blocks release of glutamate; inhibits high-voltage–activated calcium channels

LTG- Absorption, distribution

- Oral bioavailability ~98 %
- Tmax = 1-1.5 hours (4-11 hours for XR)
- Protein binding: ~55%
- V_d = 0.9-1.3 L/Kg

LTG- Metabolism, elimination

- Metabolism: **extensively metabolized in the liver** predominantly by glucuronidation (to lamotrigine 2-N-glucuronide), then excreted by the kidney
- Elimination: in urine (94%, ~90% as glucuronide conjugates and ~10% unchanged)
- **$T_{1/2}$ = ~24 hours in monotherapy; 48–60 hour with valproate; 12 hours with enzyme inducers**

LTG- Interactions

- LTG associated with mild autoinduction
- Weak inhibitor of dihydrofolate reductase
- LTG slightly increases TPM level (15%), decreases VPA level (25%)
- **LTG clearance increased in the presence of enzyme-inducing drugs, estrogen containing oral contraceptives, pregnancy**
- **LTG clearance markedly decreased by valproate**

LTG- Adverse effects

- Dose-related AEs: dizziness, ataxia, blurred vision, diplopia, nausea, and vomiting.
- Headache, tremor
- **Rash (~3%)-** higher risk in children, with co-administration of valproate, faster titration, higher dose
- **Hypersensitivity- Stevens-Johnson syndrome or TEN; hypersensitivity syndrome (~1 in 4,000)**
- **Hemophagocytic lymphohistiocytosis- very rare**
- **Recent warning of cardiac rhythm and conduction abnormalities is based on in vitro findings**

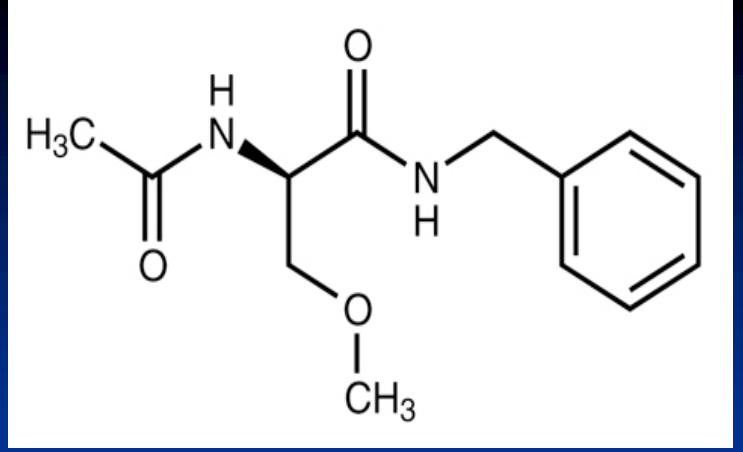
LTG- Efficacy, clinical use

- LTG is a **broad spectrum ASM** effective against focal seizures as well as generalized tonic-clonic seizures. It is indicated as adjunctive therapy for Lennox-Gastaut syndrome.
- **Efficacy against absence is less than valproate and ethosuximide**. Efficacy against myoclonic seizures is variable- it may exacerbate myoclonic seizures in some individuals.

LTG- FDA indications

- Adjunctive therapy in patients aged ≥2 for
  - Partial-onset seizures
  - Primary GTC
  - Generalized seizures of LGS
- Monotherapy- conversion to monotherapy for partial-onset seizures
- Maintenance treatment of bipolar I disorder to delay mood episode

Lacosamide (LCM)



- Approved in USA in 2008
- MOA: enhances slow inactivation of Na channels
- Available in oral and IV formulations

LCM- Absorption, distribution

- Oral bioavailability: ~100 %
- Tmax = 1-4 hours
- Protein binding: <15%
- V_d = ~0.6 L/Kg

LCM- Metabolism, elimination

- **Metabolized by demethylation in the liver to inactive O-desmethyl-metabolite via CYP-2C19**
- 95% excreted in urine (40% as unchanged drug, 30% as O-desmethyl-metabolite)
- **$T_{1/2}$ ~ 13 hours**

LCM- interactions

- Few known pharmacokinetic interactions, despite CYP-2C19 metabolism
- Serum concentration increased by cenobamate, potentially requiring dose reduction
- Pharmacodynamic interaction with other ASMs acting on sodium channel

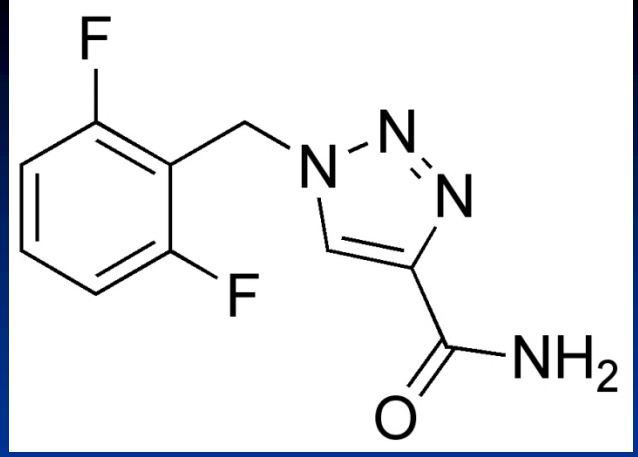
LCM- Adverse effects

- Dose-related AEs: dizziness, nausea, vomiting, diplopia, fatigue, sedation (adverse effects more likely when used in conjunction with other Na-channel blockers)
- Small, asymptomatic increase in PR interval

LCM- Efficacy, clinical use

- Effective against focal seizures and primary generalized tonic-clonic seizures; not effective against absence or myoclonic Szs, but does not usually aggravate them
- FDA indication:
  - Treatment of partial-onset seizures in patients 1 month of age and older
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older
- Greater efficacy and better tolerability if combined with a non-sodium channel drug

Rufinamide (RFM)



- Approved in USA in 2008.
- MOA: Binds to sodium channels; prolongs the inactive state of Na channels

RFM- Absorption, distribution

- Oral absolute bioavailability: ~85 % with food; less without food (food increases absorption by >30%)
- Tmax = 4-6 hours
- Protein binding: ~ 35%
- V_d = ~0.77 L/Kg

RFM- Metabolism, elimination

- Metabolism by enzymatic hydrolysis to an inactive metabolite (not dependent on p450 system)
- Elimination by excretion in urine (metabolites are inactive)
- $T_{1/2}$ = 6-10 hours

RFM- Interactions

- RFM is a weak inhibitor of CYP 2E1 (increases olanzapine level) and a weak inducer of CYP 3A4 enzymes (decreases OCP efficacy).
- RFM is a weak inducer of UDP-GT (increases clearance of LTG)
- Addition of enzyme-inducing ASMs increase RFM clearance and decrease RFM levels
- **Addition of VPA decreases RFM clearance and increases RFM levels up to 70%**

RFM- Adverse effects

- Dizziness, fatigue, somnolence, headache in adults
- Somnolence, vomiting, headache in children
- **Short QT interval**

RFM- Efficacy, clinical use

- FDA indication: adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children 1 year and older and in adults
- Efficacy against focal seizures demonstrated in trials