2023 GW Epilepsy Board Review & Best Practices

ASMs III: ASMs with multiple and miscellaneous mechanisms

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Disclosures

- Disclosure of Financial Relationships
  - None

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

ASMs with multiple and miscellaneous mechanisms

Bassel Abou-Khalil, MD

Objectives

- Review the mechanism of action of VPA, ESM, TPM, ZNS, AZM, FBM, GBP, PGB, LEV, BRV, PER, CBD, CNB, FFA
- Review pharmacokinetics of above
- Review key interactions of above
- Review main adverse effects of above
- Review clinical use of above

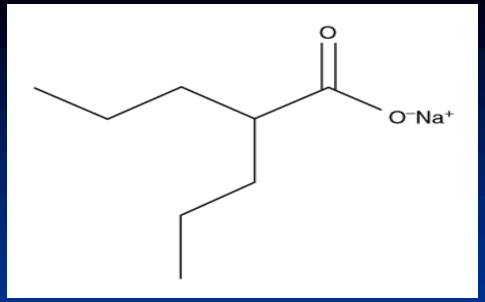
ASM main mechanisms of action

- 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

ASM with multiple and miscellaneous mechanisms

ASM	Block Na Channels	Enhancing GABA	Glutamate antagonism	T Ca channels	α2δ Ca Ch subunit	SV2A	Other	Carbonic anhydrase	Serotonin
Ethosuximide				X					
Valproate	X	X		X					
Felbamate	X	X	X						
Gabapentin/ Pregabalin					X				
Topiramate	X	X	X					X	
Zonisamide	X			X				X	
Acetazolamide								X	
Levetiracetam/ Brivaracetam						X			
Perampanel			X						
Cannabidiol		X					X		
Cenobamate	X	X							
Fenfluramine									X

Valproate- divalproex (VPA)



- Serendipitous discovery (solvent for ASMs in testing)
- Short-chain, branched fatty acid
- MOA: multiple mechanisms including blocking of Na channels, GABA potentiation, blocking T-calcium channels
- Main form used clinically is divalproex sodium, a complex of equal parts of VPA and sodium valproate

VPA- Formulations

- Formulations include:
  - Immediate-release VPA capsules, tablets, and syrup
  - Delayed release enteric coated tablets of divalproex sodium (rapid release after coating dissolved)
  - Divalproex sodium enteric-coated sprinkle capsules
  - Extended release (ER) divalproex sodium tablets
  - Parenteral sodium valproate

VPA- Absorption, distribution

- Bioavailability almost complete; 90% for ER
- **Tmax depends on preparation**
  - ~2 hrs after syrup; 3-8 hrs after enteric coated divalproex DR; 4-17 hours after divalproex ER
- V_d= 0.13-0.19 L/kg in adults; 0.20-0.30 L/kg in children
- **Protein binding ~90%; free fraction increases with increasing total concentration**
  - 30% at 150 mg/L

Example of change in protein binding with increasing concentration

	Ref Range & Units	
Valproic Acid Level Total	50 - 125 mcg/mL	97
Valproic Acid Level Free	7 - 23 mcg/mL	12
Valproic Acid Level Percent Free	5 - 18 %	12

	Ref Range & Units	
Valproic Acid Level Total	50 - 125 mcg/mL	140 ^
Valproic Acid Level Free	7 - 23 mcg/mL	35 ^
Valproic Acid Level Percent Free	5 - 18 %	25 ^

Example of change in protein binding with increasing concentration

Valproic Acid Lvl Free and Total-ARUP

Order: 298337093

Status: **Final result** Visible to patient: **Yes (seen)** Dx: **Symptomatic localization-related epil...**

0 Result Notes

Component	Ref Range & Units	3 d ago	10 mo ago
Valproic Acid Level Total	50 - 125 mcg/mL	106	140 ^
Valproic Acid Level Free	7 - 23 mcg/mL	17	35 ^
Valproic Acid Level Percent Free	5 - 18 %	16	25 ^ CM

VPA- Metabolism, elimination

- Metabolized by p450 enzyme system
- $T_{1/2}$ depends on inducing co-medication
  - Adults: 13 -16 hours without induction; 9 hours with EIASMs.
  - Children: 11.7 and 7 hours
- Most abundant metabolites glucuronide and 3-oxo-VPA.

VPA- Interactions

- Its metabolism is induced by PHT, CBZ, PB
  - Levels increase after withdrawal of EIASMs
- It can inhibit metabolism of PB, LTG, RFM, CBZ-epoxide
- **It may compete for protein binding with PHT**
- Its levels increase with co-administration of felbamate, clobazam, stiripentol

VPA- Adverse effects

- Gastric irritation with nausea, vomiting, GI distress, anorexia (less with enteric coated and ER formulation).
- Tremor
- Weight gain
- Hair loss
- Peripheral edema
- Thrombocytopenia
- Drowsiness, lethargy, confusion
- Reversible parkinsonism, dementia and brain atrophy- more in seniors
- Encephalopathy with polytherapy
- Hyperammonemia, carnitine deficiency

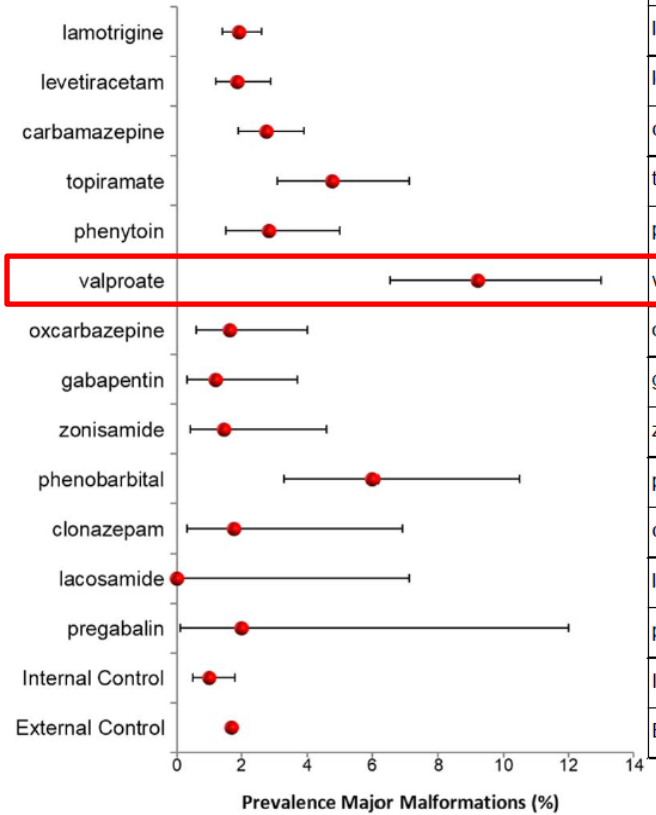
VPA- Idiosyncratic AEs

- Fatal hepatotoxicity (risk factors are polytherapy and young age- high risk with POLG mutation)
  - 1:600 at < 3 y; 1:8,000 at 3-10 y, 1:10,000 at 11-20 y; 1:31,000 at 21-40 y; 1:107,000 at >40 y
- Pancreatitis

VPA- Teratogenicity

- Dose-related teratogenicity rate higher than any other marketed AED
  - Risk of major malformations >30% at doses greater than 1100 mg/d
- In utero exposure also associated with dose-dependent reduced verbal IQ and autism

Risk of malformations for specific AED in monotherapy 1st trimester and the control groups



	N	%	95% CI
lamotrigine	2333	1.9	(1.4 to 2.6%)
levetiracetam	1179	1.9	(1.2 to 2.9%)
carbamazepine	1122	2.8	(1.9 to 3.9%)
topiramate	503	4.8	(3.1 to 7.1%)
phenytoin	423	2.8	(1.5 to 5.0%)
valproate	336	9.2	(6.5 to 13%)
oxcarbazepine	304	1.6	(0.6 to 4.0%)
gabapentin	251	1.2	(0.31 to 3.7%)
zonisamide	205	1.5	(0.4 to 4.6%)
phenobarbital	200	6.0	(3.3 to 10.5%)
clonazepam	113	1.8	(0.3 to 6.9%)
lacosamide	64	0.0	(0 to 7.1%)
pregabalin	50	2.0	(0.1 to 12%)
Internal Control	1201	1.0	(0.5 to 1.8%)
External Control	289,365	1.7	

Jan 2023

VPA- Efficacy and clinical indications

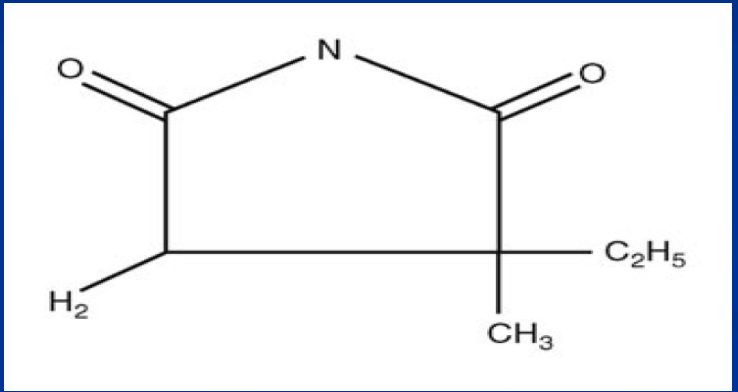
- **Official FDA indication is for generalized absence and partial-onset seizures**
- **Broad spectrum of efficacy against focal and all generalized-onset seizures, including myoclonic seizures.**
- **Most effective ASM for IGE with generalized tonic-clonic seizures, but should be avoided in women of child-bearing potential**
- Also indicated for migraine prophylaxis and bipolar disorder

Comparison of VPA with CBZ for treatment of complex partial and secondarily generalized tonic-clonic seizures in adults

Mattson et al, NEJM 1992

- Multicenter, DB trial of VPA vs CBZ in 480 adults with CPS or SGTCS
- Patients randomly assigned to CBZ or VPA at doses adjusted to achieve blood levels in the mid-therapeutic range.
- Patients followed for 1-5 years, until seizures became uncontrollable, treatment had unacceptable adverse effects, or both.
- **For control of SGTC, CBZ and VPA were comparably effective**.
- **For CPS, 4/5 measures favored CBZ**: total # of seizures, # of seizures per month, time to first seizure, and seizure-rating score.
- CBZ was superior according to a composite score of seizure control and adverse effects. VPA was associated with weight gain >12 lb, hair loss, and tremor. Rash was more common with CBZ.
- **VPA is as effective as CBZ for treatment of SGTC, but CBZ provides better control of CPS and has fewer long-term adverse effects.**

Ethosuximide (ESM)



- MOA: **blockade of T-type calcium currents in thalamus**

ESM- Absorption, distribution

- **Oral bioavailability 90% to 95%**
- Tmax= 1-4 hours
- Vd= 0.65 L/Kg
- **Protein binding: <10%**

ESM- Metabolism, elimination

- Extensive hepatic oxidative biotransformation to inactive metabolite by CYP3A>> CYP2El.
- **$T_{1/2}$= 30-60 hours** (shorter in children)

ESM- Interactions

- No effect on hepatic p450 enzymes and low protein binding predict low potential for causing interactions.
  - reduced VPA level in one study
- Susceptible to interactions from inducers and inhibitors of p450 enzyme system.
  - Clearance increased with enzyme inducers
  - Clearance may decrease with VPA, isoniazid

ESM- Adverse effects

- Most AEs are dose related- helped by dividing dose and administration with meals
  - Nausea, abdominal discomfort, anorexia, vomiting and diarrhea
  - Drowsiness, insomnia, nervousness, dizziness, hiccups, fatigue, ataxia, and behavior changes (aggression, irritability, hyperactivity)
  - Granulocytopenia
- Headaches, psychosis, depression, hallucinations (visual or auditory) not clearly dose related

ESM- Idiosyncratic AEs

- Rash, Stevens-Johnson syndrome, SLE
- Aplastic anemia, thrombocytopenia, agranulocytosis (rare)
- Autoimmune thyroiditis (rare)

ESM- Efficacy and clinical indications

- **First-line monotherapy against typical absence seizures**
- Comparative trial favored its tolerability over valproate and efficacy over lamotrigine
- Narrow spectrum ASM- not effective against any other seizure type

ESM- Monitoring

- Therapeutic range: 40-100 mg/L
- CBC can be checked before and after 2-3 months of treatment. Continued routine monitoring of CBC not useful.
- CBC should be obtained if there are signs or symptoms of infection. If the WBC count < 3.5 K or granulocytes less than 25% of the total WBC count, consider reducing ESM dose

Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy

Glauser et al, NEJM 2010

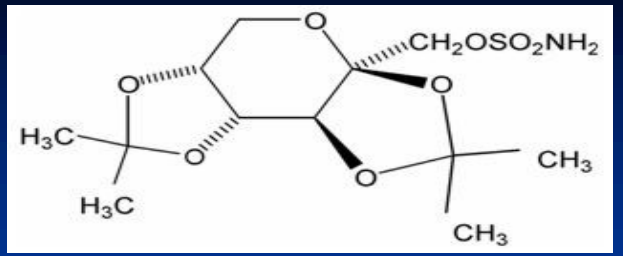
- **Double-blind, randomized, controlled clinical trial to compare the efficacy, tolerability, and neuropsychological effects of ethosuximide, valproic acid, and lamotrigine** in 453 children with newly diagnosed childhood absence epilepsy
- ASM doses were increased until child was free of seizures, maximal allowable or highest tolerable dose was reached, or a criterion indicating treatment failure was met
- **The primary outcome measure was freedom from treatment failure after 16 weeks of therapy**
- **Secondary outcome measure was attentional dysfunction**

Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy- Results

Glauser et al, NEJM 2010

- 453 children randomly assigned to ethosuximide (156), lamotrigine (149), or valproic acid (148)
- **After 16 weeks of therapy, freedom-from-failure rates for ethosuximide and valproic acid were similar (53% and 58%, respectively) and higher than the rate for lamotrigine (29%)**
- There were no significant differences among the three drugs in discontinuation because of adverse events
- **Attentional dysfunction more common with valproic acid than ethosuximide** (in 49% vs. 33% of the children; P=0.03)
- **Ethosuximide and valproic acid more effective than lamotrigine in treatment of childhood absence epilepsy. Ethosuximide associated with fewer adverse attentional effects**

Topiramate (TPM)



- Sulfamate-substituted monosaccharide
- Approved in USA in 1996.
- MOA: **multiple mechanisms**, including
  - blocking of voltage-gated sodium channels
  - augmentation of GABA activity
  - antagonism of AMPA/kainate receptors
  - inhibition of high-threshold activated Ca channels
  - weak inhibition of carbonic anhydrase activity

Carbonic anhydrase inhibition

- Increases carbon dioxide, which may increase seizure threshold.
- Increase in brain carbon dioxide has been associated with an increase in GABA.
- Likely a minor mechanism

TPM- Absorption, distribution

- Oral bioavailability ~80-95 %
- Tmax = 1.5-4 hours
- Protein binding: 15-40%
- V_d = ~0.7 L/Kg

TPM- Metabolism, elimination

- Metabolism: **not extensively metabolized**
- **70% eliminated unchanged in the urine**
- hepatic metabolism by P450 enzyme system- metabolites formed via hydroxylation, hydrolysis, and glucuronidation.
- There is **evidence of renal tubular reabsorption**
- $T_{1/2}$ = ~21 hours

TPM- Interactions

- Drug interactions are minimal.
- Enzyme inducing ASMs may reduce TPM levels by up to 50%
- **Mild inhibitor of CYP2C19** (may increase PHT levels at higher dose) and a **mild inducer of CYP3A4** (may decrease OCP efficacy at dose ≥200 mg/day)
- **May cause hyperammonemia when co-administered with VPA**

TPM- Adverse effects

- Sedation, fatigue, dizziness, ataxia (helped by slower titration)
- **Memory disturbance; word finding difficulty; cognitive slowing- patients may not be aware of these**
- Depression
- Kidney stones (1.5%)
- **Acute myopia and secondary angle closure glaucoma**
- **Paresthesias** (decrease over time- helped by K supplementation)
- **Oligohydrosis**, hyperthermia (in children)
- **Metabolic acidosis**
- Weight loss
- Increased risk of birth defects in exposed infants, mainly oral clefts- lip or palate; low birth weight

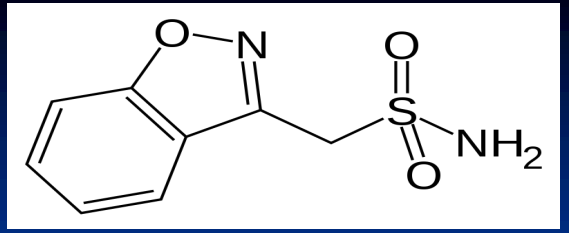
TPM- Clinical use and efficacy

- **Broad spectrum ASM, but not effective against absence** in a controlled randomized trial
- FDA indications:
  - Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures
  - Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with LGS
  - Prophylaxis of migraine in adults and adolescents ≥12 years
- **Requires slow titration to improve tolerability** (25 mg/wk, up to 100-400 mg)

TPM- Monitoring

- Suggested therapeutic range: 5–20 mg/L

Zonisamide (ZNS)



- Structurally related to sulfonamides
- Approved in Japan in 1989. First approved in the USA in 2000.
- MOA: **multiple mechanisms:** blocks sodium channels (blocks sustained repetitive firing), **reduces T-type Ca currents**, weakly inhibits carbonic anhydrase (100-200 times less potent than acetazolamide)

ZNS- Absorption, distribution

- Oral absolute bioavailability: ~100 %
- Tmax = 2-5 h after oral dosing, 4-6 h with food
- Protein binding: 40-50%
- V_d = 0.9–1.4 L/kg

ZNS- Metabolism, elimination

- **Hepatic metabolism** by acetylation and reduction (mediated by CYP 3A4), then glucuronidation- metabolites inactive
- Cleared by renal excretion
- **$T_{1/2}$ = ~ 60 hours**

ZNS- Interactions

- Not a hepatic enzyme inducer or inhibitor- has no effect on pharmacokinetics of other commonly used ASMs
- **Affected by CYP 3A4 inducers or inhibitors**
  - Addition of enzyme-inducing ASMs decreases ZNS half-life and plasma level
  - ZNS concentration increased by CYP3A4 inhibitors (e.g. ketoconazole, cyclosporine)

ZNS- Adverse effects

- Sedation, ataxia, dizziness, nausea, anorexia, fatigue, agitation/irritability
- Weight loss
- **Cognitive slowing**, difficulty with concentration
- **Kidney stones** (up to 4%)
- Depression, psychosis
- Rare serious rash (SJS and TEN)
- **Oligohydrosis and hyperthermia** (in children)
- Metabolic acidosis

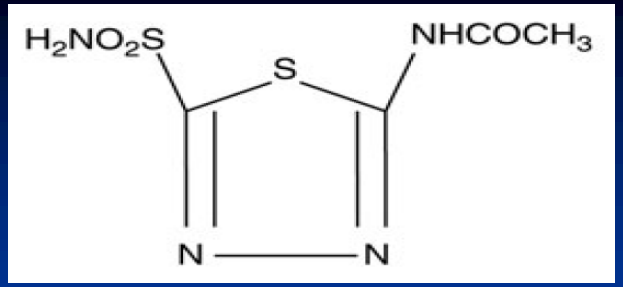
ZNS- Efficacy/clinical indication

- Broad spectrum agent; class I trials only for focal epilepsy
- FDA indication: adjunctive therapy in the treatment of partial seizures in adults with epilepsy
- In Europe it is indicated as initial monotherapy for partial seizures. In Japan it is also indicated as monotherapy for generalized seizures (tonic, tonic-clonic, and atypical absence)
- Start at 100 mg daily, titrate Q 2 weeks- long $T_{1/2}$ allows once daily dosing off label

ZNS- Monitoring

- Suggested therapeutic range: 10-40 mg/L

Acetazolamide (AZM)



- Carbonic anhydrase inhibitor
- **Bioavailability complete with low dose, decreases with increasing dose**
- Tmax= 2–4 hrs
- **Protein binding: 90–95%**
- V_d: 1.8 L/kg
- $T_{1/2}$= 10–12 h
- Partially metabolized; 80% excreted by tubular secretion

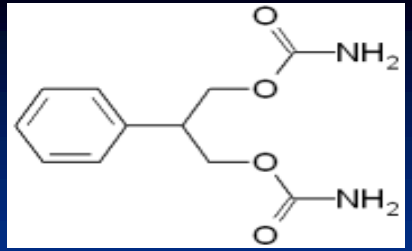
AZM- Adverse effects

- Altered taste perception (flat), loss of appetite, drowsiness, paresthesias
- Renal stones particularly in combination with topiramate, zonisamide, or ketogenic diet
- Metabolic acidosis
- Rare idiosyncratic: rash, hypersensitivity reactions, Steven Johnson syndrome, toxic epidermal necrolysis
- Rare muscle weakness, hepatic dysfunction

AZM- Clinical use

- Adjunctive therapy for refractory focal and generalized epilepsies, particularly absence [FDA indication centrencephalic epilepsies (petit mal, unlocalized seizures)]
- Adjunctive therapy for catamenial epilepsy, starting 2 days before predicted exacerbation
- Start at 250 mg/day and increase weekly based on response, up to 500–1,000 mg/day in 2-3 divided doses.
- Evidence for efficacy class 4 or anecdotal.

Felbamate (FBM)



- Approved in USA in 1993.
- FDA indication: monotherapy or adjunctive therapy for partial epilepsy in adult and pediatric patients, adjunctive therapy for Lennox-Gastaut syndrome
- MOA: **NMDA antagonism**, enhancing GABA, blocking sodium channels, blocking high voltage activated calcium channels

FBM- Absorption, distribution, metabolism

- Oral bioavailability: >90%
- Tmax = 2-6 hours
- Protein binding: ~25%
- V_d = ~0.75 L/Kg
- Metabolism: hepatic via CYP3A4
- 40-50% of absorbed dose appears unchanged in urine, and the rest as inactive metabolites and conjugates.
- $T_{1/2}$ = **20-23 hours,** shorter in children/ w enzyme induction

FBM- Interactions

- FBM is an **inhibitor of CYP2C19**, CYP1A2, and ß-oxidation
  - Inhibits metabolism and increases levels of PB, PHT, VPA, CBZ-epoxide, N-CLB, coumadin
- FBM **induces CYP3A4**
  - Decreases CBZ level
  - Decreases OCP efficacy
- Enzyme-inducing ASMs decrease FBM level

FBM- Adverse effects

- Common:
  - Anorexia, nausea, vomiting, weight loss
  - Insomnia, irritability, headache
- Serious idiosyncratic
  - **Aplastic Anemia** (estimated risk 1 in 5,000-8,000, not reported below age 13)- onset after 2.5-6 months
    - Risk factors: prior cytopenia, allergy or significant toxicity to an ASM, underlying autoimmune disease.
  - **Hepatic Failure** (estimated risk: 1 in 26,000-34,000)- onset after 25-939 days (mean 217)

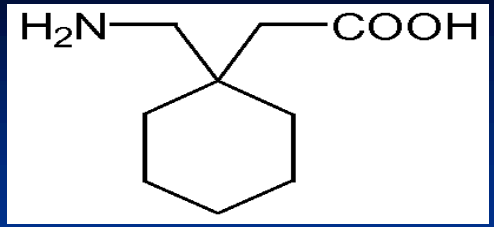
FBM- Efficacy, clinical use

- Broad spectrum ASM
- FDA indications:
  - not indicated as a first line treatment.
  - recommended only in those who respond inadequately to alternative treatments and whose epilepsy is so severe that risk of aplastic anemia and/or liver failure is deemed acceptable.
  - written, informed consent
  - either monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children.

FBM- Monitoring

- CBC and LFTs should be obtained prior to starting FBM, monitored regularly, Q2 weeks initially, Q 2-3 months after 6 months, then every 6 months after the first year.
- Felbamate suggested therapeutic range: 40-100 mg/L

Gabapentin (GBP)



- Approved in USA in 1994
- FDA indications:
  - adjunctive therapy in adult and pediatric (≥3 years) patients for partial seizures
  - management of postherpetic neuralgia in adults
- MOA: binds to α2δ subunit of voltage-gated Ca channels (reducing influx of calcium and reducing neurotransmitter release under hyper-excitable conditions)
- No interaction with GABA receptors

GBP- Absorption, distribution

- **Transport into blood by L-amino acid transport system, which is saturable**
- **Oral bioavailability low**, with considerable inter-subject variability, and **decreases with increasing GBP dose** (60% after 300 mg, 29% for 1600 mg tid, 36% for 1200 mg Qid)
- Antacids taken within 2 hours before GBP may decrease GBP bioavailability by up to 20%
- Tmax = 2-3 hours
- **Protein binding: <3%**
- V_d = 0.6-0.8 L/Kg

GBP- Metabolism, elimination, interactions

- **Not metabolized in humans**
- **Eliminated unchanged in the urine**
- $T_{1/2}$ = 5-7 hours
- Requires dose reduction with renal impairment
- No known interactions (predicted by absence of metabolism, absence of enzyme induction or inhibition, and absence of protein binding)

GBP- Adverse effects

- Sedation
- Dizziness, ataxia, asthenia
- Weight gain
- **Myoclonus**
- Cognitive slowing in elderly
- Emotional lability, hostility in children

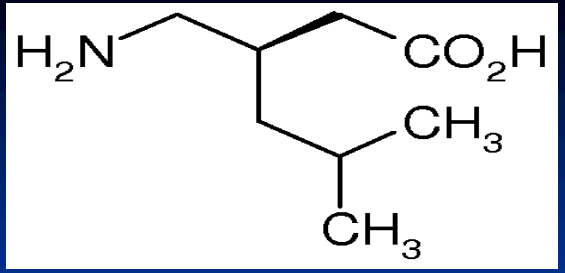
GBP- Efficacy, clinical use

- Under-dosed in clinical trials- dose can go to 4800 mg per day (3-4 divided doses)
- Narrow spectrum agent against focal seizures
- **Failed trials against absence and 1ary GTC seizures**
- May cause exacerbation of myoclonic seizures
- FDA approved for adjunctive therapy for partial seizures and for postherpetic neuralgia- extended release preparation (GBP enacarbil) for RLS and another (gastroretentive dosage form) for postherpetic neuralgia
- Primarily used off label for pain and other nonepileptic indications

GBP- Monitoring

- Optimal therapeutic plasma concentration not established
- Suggested therapeutic plasma concentration range: 2–20 mg/L

Pregabalin (PGB)



- Approved in USA in 2005
- MOA: binds to α2δ subunit of voltage-gated Ca channels (reducing influx of calcium and reducing neurotransmitter release under hyper-excitable conditions)

PGB- Absorption, distribution, metabolism

- Oral bioavailability: ≥90 %, **independent of dose**
- Tmax = 1 hours (delayed to 3 hours with food)
- **Protein binding: none**
- **Not metabolized in humans**
- Excreted unchanged in the urine (requires dose reduction with renal impairment); $T_{1/2}$ = ~ 6 hours
- No known pharmacokinetic interactions

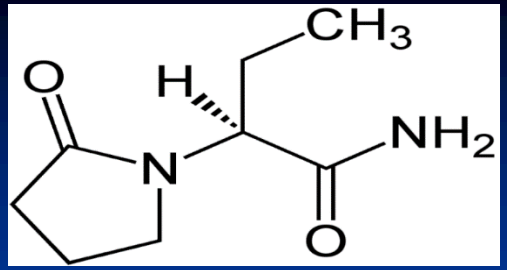
PGB- Adverse effects

- Somnolence
- Dizziness, ataxia, blurred vision, asthenia
- **Increased appetite, weight gain**
- **Peripheral edema**
- **Myoclonus**

PGB- Efficacy, clinical use

- **Narrow spectrum against focal-onset seizures**
- FDA indications:
  - Adjunctive therapy for partial onset seizures age ≥1 month
  - Neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia, fibromyalgia, neuropathic pain associated with spinal cord injury
- Optimal therapeutic level unknown. Range of concentration at effective doses of 300-600 mg per day: 2.8–8.2 mg/L

Levetiracetam (LEV)



- Approved in USA in 1999
- MOA: **binding to the synaptic vesicle protein SV2A**
  - seems to result in nonspecific decrease in neurotransmitter release.
  - functional correlation between SV2A binding affinity and anticonvulsant potency of levetiracetam analogs
- Available in oral and IV formulations.

LEV- Absorption, distribution, metabolism

- Oral absolute bioavailability ~100 %
- Tmax = ~1 hour (1.5 hours with food)
- **Protein binding: <10%**
- V_d = ~0.6 L/Kg
- **No hepatic metabolism**
- Partly hydrolyzed to inactive compounds
- 66% excreted unchanged in the urine
- $T_{1/2}$ = 6-8 hours (shorter in children, longer in the elderly)

LEV- Interactions

- No known significant pharmacokinetic interactions
- Some studies have suggested lower LEV levels in presence of enzyme inducers

LEV- Adverse effects

- Somnolence
- Dizziness, asthenia
- **Irritability**, hostility (more common in children)- pyridoxine supplementation may be helpful anecdotally
  - Risk factors for behavioral adverse effects: symptomatic generalized epilepsy, history of psychiatric diagnosis, faster LEV titration
- Rare psychosis

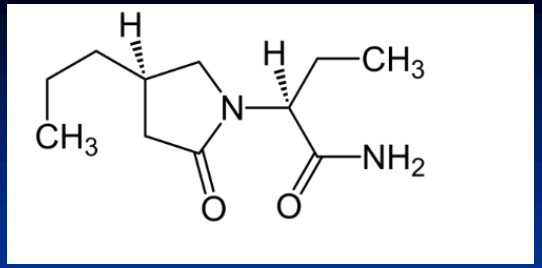
LEV- Efficacy, clinical use

- Broad spectrum agent
- Official FDA indications:
  - adjunctive therapy for partial onset seizures in adults and children ≥ 1 month.
  - adjunctive therapy for myoclonic seizures in adults and adolescents ≥ 12 years with juvenile myoclonic epilepsy.
  - adjunctive therapy for primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age and older with idiopathic generalized epilepsy.
- Approved for initial monotherapy in Europe

LEV- Monitoring

- Optimal therapeutic level unknown
- One study suggested 11 mg/L may be a threshold concentration for a therapeutic response. Upper limit of therapeutic range unknown.

Brivaracetam (BRV)



- Approved in USA in 2016
- MOA: binding synaptic vesicle protein 2A (SV2A) with ~20-fold higher affinity for than levetiracetam
- Higher brain permeability than levetiracetam
- Broad spectrum in preclinical models

BRV- Pharmacokinetics

- Bioavailability ~100%
- Weakly bound to plasma proteins (~17.5%)
- Half-life ~ 9 h
- Renally excreted following extensive metabolism, primarily by hydrolysis and to a lesser extent by CYP-dependent hydroxylation (main isoenzyme responsible for hydroxylation is CYP2C19)

BRV - Interactions

- Enzyme inducers (PHT, CBZ, PhB) reduce BRV levels
- BRV may increase CBZ-epoxide; may increase PHT concentration by up to 20%

BRV- Clinical Studies

- 100 and 200 mg doses more effective than placebo for all outcome measures; responder rates 38.9 and 37.8% (Klein et al, 2015)
- 20 and 50 mg efficacy inconsistent across studies
- Not effective in patients taking levetiracetam
- Efficacy numbers better in levetiracetam naïve patients that in patients who failed levetiracetam (but could be because latter group is more drug-resistant)

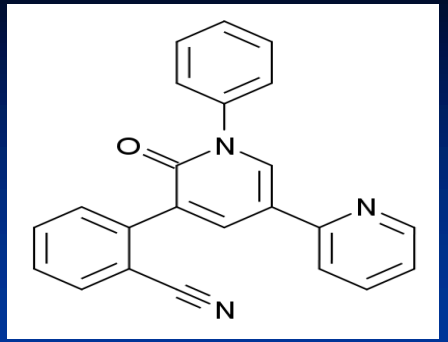
BRV- Adverse effects

- Somnolence, dizziness and fatigue most common AEs
- The incidence of irritability was 0.4% PBO; 3.2% BRV 100 mg/day, 2.8% BRV 200 mg/day
- Several studies demonstrated improvement in behavioral adverse effects in individuals switched from levetiracetam

BRV - Clinical Use

- Broad spectrum agent (but only approved for focal seizures)
- FDA indication: treatment of partial-onset seizures in patients ≥ 1 month (FDA extrapolation policy).
- Available in oral tablets (10, 25, 50, 75, 100 mg), oral solution (10 mg/ml), injection (10 mg/ml) for oral replacement
- Injection is FDA approved only in adult patients (≥16 years of age)

Perampanel (PER)



- Approved in USA in 2012
- MOA: noncompetitive antagonism of AMPA glutamate receptor

PER- Absorption, distribution

- Oral absolute bioavailability: ~100%
- Tmax = 1 hour
- **Protein binding: ~95%**
- V_d= ~77 L

PER- Metabolism, elimination

- Extensively metabolized by primary oxidation mediated by CYP3A followed by glucuronidation
- Excretion: as inactive metabolites, 30% in the urine and 70% in the feces.
- $T_{1/2}$ = **105 hours** (average).

PER- Interactions

- PER does not have a clinically significant effect on other ASMs
- PER dose of 12 mg (not 8 mg) reduces levonorgestrel by ~40%
- Enzyme-inducers decrease PER levels

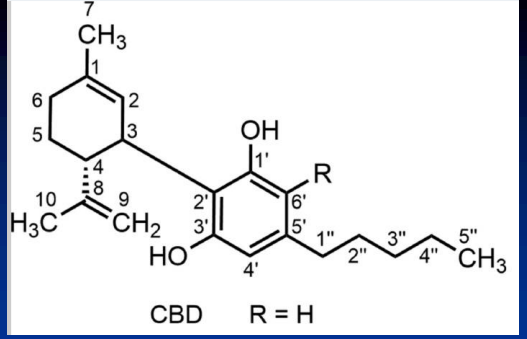
PER- Adverse effects

- Dizziness, somnolence, headache, fatigue, ataxia, blurred vision most common
- Aggression, hostility (black box warning- 20% at 12 mg)

PER- Efficacy and clinical use

- Broad spectrum agent
- FDA indication
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥4 years
  - Adjunctive therapy for primary generalized tonic-clonic seizures in patients with epilepsy ≥12 years
- Case series suggest potentially dramatic efficacy in progressive myoclonic epilepsies, with efficacy against action myoclonus

Cannabidiol (CBD)



- First marketed in the USA in 2018.
- Cannabinoid, but does not interact with cannabinoid receptor CB1
- Does not share THC psychoactive properties
- May enhance GABA activity through allosteric modulation of the $GABA_A$ receptor and enhancement of currents elicited by low GABA concentrations
- Modulates intracellular calcium

CBD- Absorption, distribution

- Oral bioavailability is low: administration with a high-fat/high-calorie meal increased Cmax by 5-fold, AUC by 4-fold
- Tmax = 2.5 to 5 hours
- **Protein binding: >94%**

CBD- Elimination

- Extensively metabolized primarily in the liver by CYP2C19 and 3A4, and UGT1A7, 1A9, and 2B7, to an active (7-OH-CBD) and then inactive metabolite (7-COOH-CBD)
- Excretion: in feces, with minor renal clearance.
- $T_{1/2}$= 56-61 hours

CBD- Interactions

- CBD clearance is increased by CYP2C19 and CYP3A4 inducers and decreased by inhibitors
- Potential to inhibit CYP2C8, CYP2C9, and CYP2C19 as well as UGT1A9 and UGT2B7
- Most important interaction is with clobazam
  - CBD increased clobazam active metabolite, N-desmethylclobazam up to 3-fold
  - CLB increased CBD active metabolite 7-OH CBD
- No interaction with valproate

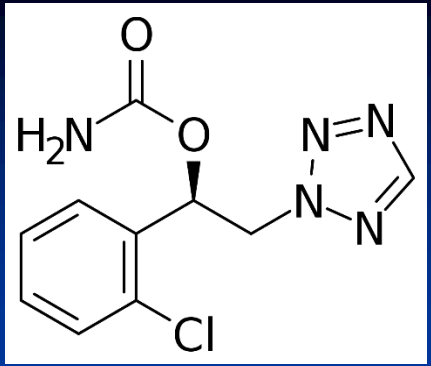
CBD- adverse effects

- Sedation, fatigue
- Decreased appetite, diarrhea
- Increased liver enzymes, particularly when used with valproate
  - check liver enzymes, bilirubin before, and 1, 3, and 6 months after starting treatment

CBD- efficacy, clinical indications

- FDA indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older based on blinded controlled trials.
- Open-label trials also suggest efficacy for other forms of epilepsy.
- Artisanal cannabidiol formulations are used without prescription by many patients with epilepsy in the United States.

Cenobamate (CNB)



- Approved in 2019
- MOA:
  - Sodium channel antagonism, preferentially attenuating the persistent sodium current
  - Enhancing GABA through positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel

CNB- Absorption, distribution

- Oral absolute bioavailability: ~88%
- Tmax = 1-4 hour
- **Protein binding: ~60%**
- V_d= ~40-50 L

CNB- Metabolism, elimination

- Extensively metabolized by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5.
- Excretion: 87% in urine, mostly as inactive metabolites- 6.4% unchanged
- $T_{1/2}$ = **50-60 hours**.

CNB- Interactions

- Phenytoin, an enzyme inducer, reduces CNB level
- CNB inhibits **CYP2C19 (increased concentrations of phenytoin, phenobarbital, N-desmethylclobazam)**
- CNB induces **CYP3A4 (affects oral contraceptives, carbamazepine),** CYP2B6
- CNB decreases lamotrigine concentration
- CNB not a substrate for drug transporter proteins

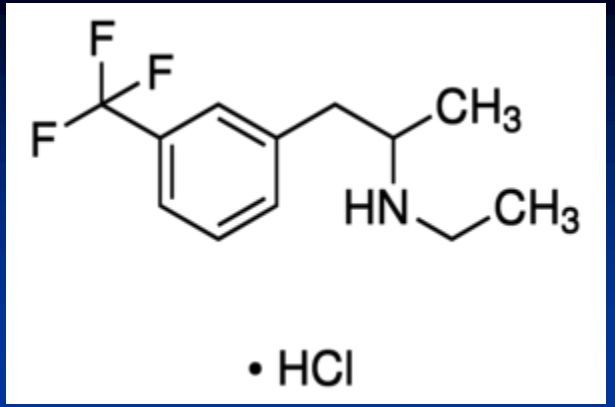
CNB- Adverse effects

- Somnolence, dizziness, fatigue, ataxia, diplopia, headache
- Rare cases of DRESS syndrome, not seen after slowing the titration rate

CNB- Efficacy and clinical use

- FDA indication
  - Treatment of partial-onset seizures in adult patients
- Unusual efficacy against focal seizures
  - Seizure-free rate: study 1: 27.5% CNB 200 mg vs 9.1% placebo; study 2: 11% CNB 200 mg, 21% CNB 400 mg vs 1% placebo
- Slow titration required: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, with 2 weeks for each step; the dose can be increased again by 50 mg every 2 weeks, up to 400 mg per day

Fenfluramine (FFA)



- Repurposed medication, originally an appetite suppressant in the 1970s, withdrawn because of reports of heart valve abnormalities and pulmonary hypertension.
- Increases serotonin by disrupting its vesicular storage and reversing serotonin transporter function. Its active metabolite binds to and activates serotonin receptors.

FFA- absorption, distribution, metabolism

- Oral bioavailability 68-74%
- Vd= 11.9L/Kg
- Protein binding: 50%
- Tmax 3-5 hours
- Protein binding: 50%
- Metabolized to the active metabolite norfenfluramine (75%), which is then converted to inactive metabolites.
- T1/2= ~20 hours.
- Coadministration with stiripentol and clobazam increases its plasma concentration

FFA- Adverse effects

- Decreased appetite, fatigue, somnolence, and weight loss
- Valvular disease or pulmonary hypertension have not been observed in pediatric epilepsy studies, possibly because lower doses were used than for appetite suppression and because of the younger age of epilepsy patients compared with those treated for obesity in the past

FFA- Clinical indication

- Treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients ≥2 years