2023 GW Epilepsy Board Review & Best Practices

ASMs II: The GABA System

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Disclosures

- Disclosure of Financial Relationships
  - None

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

ASMs acting on the GABA system

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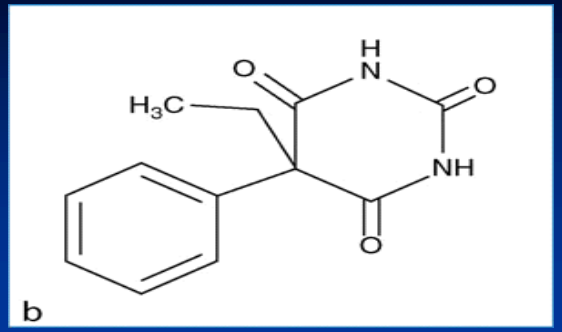
Objectives

- Review the mechanism of action of GABA-acting antiseizure medications
- Review pharmacokinetics of drugs with main mechanism related to GABA
- Review key interactions of above ASMs
- Review main adverse effects of above ASMs
- Review clinical use of above ASMs

Enhancing GABA as a mechanism of ASM action

- **Irreversible inhibition of GABA transaminase: vigabatrin**
- **Inhibition of GABA reuptake at the synapse: tiagabine**
- **Prolongation of GABA-mediated chloride channel openings: phenobarbital**
- **Increased frequency of GABA-mediated chloride channel openings: benzodiazepines**, topiramate (different binding site)
- Other: valproate, felbamate, cannabidiol, stiripentol, cenobamate, ganaxolone
- Some ASMs are associated with acute elevation of brain GABA by MRS after single doses: 70% for topiramate, 48% with gabapentin (but gabapentin does not interact with the GABA receptor).

Phenobarbital (PB)



- In use since 1912
- MOA: **enhances postsynaptic $GABA_A$ receptor-mediated chloride currents, prolonging the opening of the Cl^- channel.** May also have other actions (HVA Ca channels and glutamate receptors).
- Available as oral preparations and parenteral solution

PB- Absorption, distribution

- **Oral absolute bioavailability is > 90%**
- Tmax = 2-4 hours
- **Protein binding: ~45%**
- V_d = ~0.6 L/Kg

PB- Elimination

- Elimination: **20-25% eliminated renally, unchanged; rest metabolized in the liver**
- $T_{1/2}$ = **80-100 hours in adults;** ~100-150 hours in newborns; 60-70 hours after that, before age 5

PB- Interactions

- PB is a **potent inducer of p450 enzymes**. Accelerates metabolism and reduces levels of ASMs processed by this enzyme system
  - Reduces levels of valproate, ethosuximide, lamotrigine, etc..
  - Reduces levels of CBZ (but may increase CBZ-epoxide to CBZ ratio)
  - Reduces efficacy of warfarin, steroids, oral contraceptive
  - Variable effect on phenytoin (due to competition for metabolism)
- Phenobarbital **level is increased by inhibitors valproate, felbamate, cenobamate**

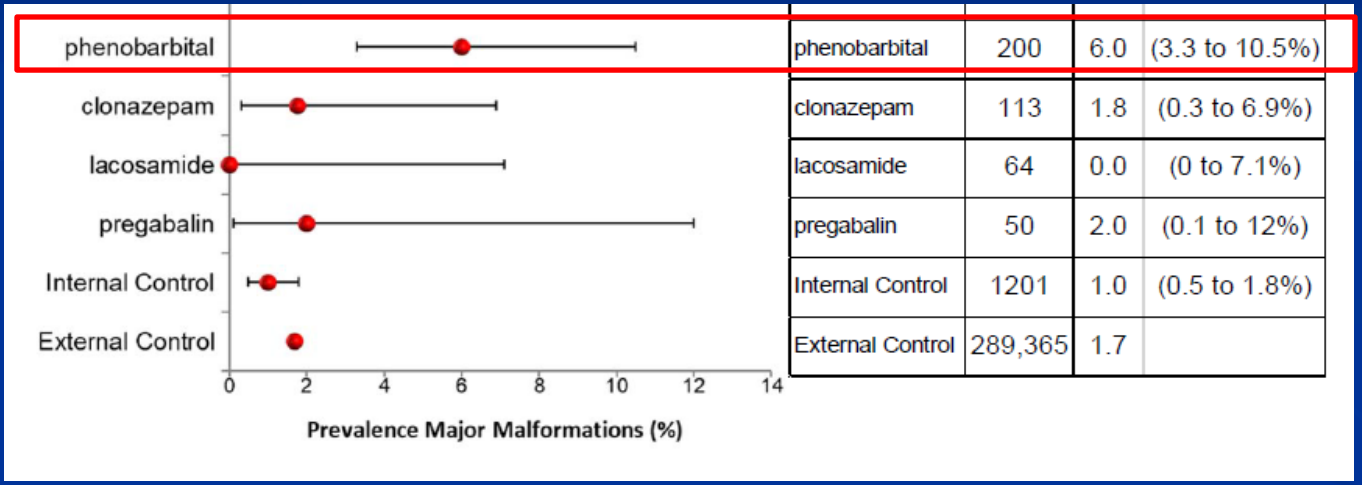
PB- Adverse effects

- Sedation
- Mood changes (depression)
- Hyperactivity/irritability in children
- Decreased memory and concentration
- Long term use associated with decreased bone density and connective tissue disorders
  - Dupuytren's contractures
  - Plantar fibromatosis
  - Frozen shoulder

PB- Efficacy/clinical indication

- Effective against focal seizures, generalized tonic-clonic seizures, other generalized-onset seizures except absence.
- IV preparation may be used against status epilepticus
- Not drug of choice in developed countries
- May be the only affordable ASM in much of the developing world

PB- Teratogenicity



	N	%	95% CI
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	

North American AED Pregnancy Registry
Rate of major malformations in monotherapy- Jan 2023 data

- Increased risk of cardiac malformations
- Reduced cognitive abilities in exposed male offspring

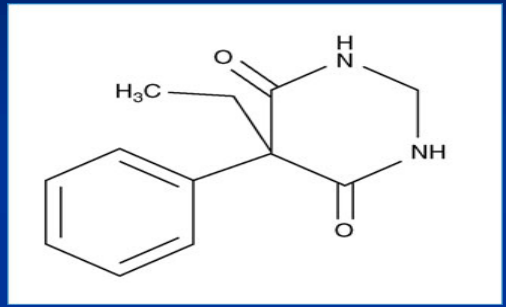
PB- Monitoring

- “Therapeutic” concentration: 15-40 mg/L

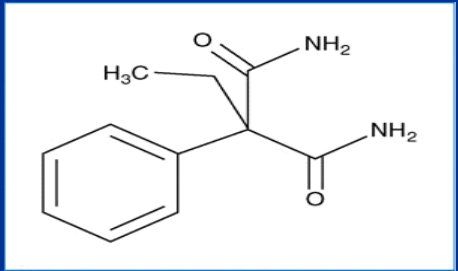
Primidone (PRM)

- Converted to phenobarbital (PB) and active metabolite phenyl-ethyl-malonamide (PEMA)
- MOA:
  - Does not have a direct effect on GABA receptors.
  - PB acts on the $GABA_A$ receptor to prolong opening of the chloride channel
  - PRM acts synergistically with PB to reduce sustained, high-frequency, repetitive firing at clinically relevant concentrations
- PEMA action unknown and modest

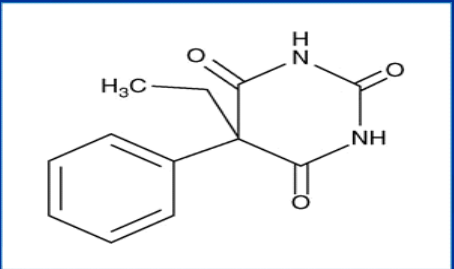
Primidone



Phenylethylmalonamide (PEMA)



Phenobarbital



PRM- Absorption, distribution

- **Oral bioavailability is fairly complete (~92%)**
- Tmax = ~3 h
- V_d = 0.54 (single dose)-0.86 L/Kg
- **Poorly soluble, precluding IV preparation**
- **Protein binding: <10%** for PMD and PEMA

PRM- Metabolism and elimination

- **PEMA is first detected metabolite**
- **~25% of oral PRM is converted to PB** (dose of PRM required for certain PB level ~4-5 x dose of PB required for same level)
- In monotherapy $T_{1/2}$= 10-15 hours- with enzyme inducers $T_{1/2}$= 6.5-8.3 hours.
- After one dose 64% excreted unchanged in absence of induction, ~40% excreted unchanged with induction.

PRM- Interactions

- Co-administration of inducers (particularly PHT) reduces ratio of PRM to PB due acceleration of PRM to PB conversion.
- PRM and PB are potent enzyme inducers
- All PB interactions are present by necessity

PRM- Adverse effects

- **Acute toxic reactions different from PB**
  - Transient drowsiness, dizziness, ataxia, nausea, and vomiting that can be debilitating.
  - Tolerance to acute AEs develops rapidly within hours to days.
  - Long-term PB therapy protects from acute PRM toxicity
- Chronic AEs same as PB

PRM- Efficacy and indications

- Effective against same seizure types as phenobarbital
- Equal efficacy, but lower tolerability in comparison to PB, PHT, CBZ

PRM- Monitoring

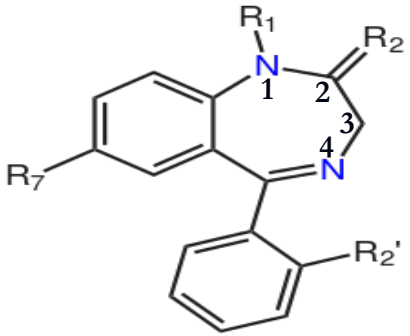
- "Therapeutic plasma concentration" of PRM 5-12 mg/L.
- Phenobarbital level may also be monitored (15-40 mg/L)
- Since ~25% of oral PRM is converted to PB, dose of PRM required for certain PB level ~4-5 x dose of PB required for same PB level

Comparison of CBZ, PHB, PHT, or PMD in partial and secondarily generalized tonic-clonic seizures Mattson et al, NEJM 1985

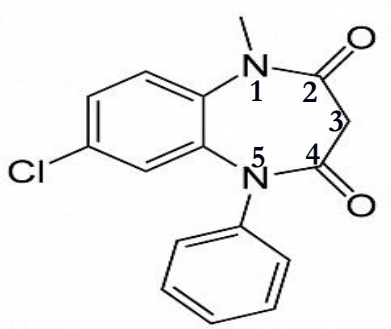
- 10-center, DB trial to compare efficacy and toxicity of four ASMs [carbamazepine (CBZ), phenobarbital (PHB), phenytoin (PHT), or primidone (PMD)] in partial and secondarily generalized tonic-clonic seizures (SGTCS)
- 622 adults patients randomly assigned to CBZ, PHB, PHT, or PMD and followed for 2 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**
- **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."

Benzodiazepines

- Mechanism of action: Increased frequency of GABA-mediated chloride channel openings



Most benzodiazepine



Clobazam

Benzodiazepines

- **Diazepam, lorazepam, midazolam** primarily used for acute seizure emergencies (status epilepticus and acute repetitive seizures)
- **Clonazepam**, **clorazepate**, **clobazam** used mainly for chronic epilepsy management

Benzodiazepines- Absorption and distribution pharmacokinetics

- Most benzodiazepines have oral bioavailability >80% (except 40% for midazolam, due to metabolism in intestinal epithelium).
- All benzodiazepines rapidly cross BBB, diffusion rate and onset of action determined by lipid solubility.
- Large volumes of distribution, characterized by two-compartment model.
- Highly protein bound.

Distribution by one vs ≥2 compartment model

- A one-compartment distribution model exists if the final concentration equilibrium is reached rapidly following IV administration
- ≥2 compartment distribution model applies if after initial rapid distribution in one compartment the drug diffuses into a second or more compartments.
- The total V_d will correspond to the sum of the compartments.
- An example is diazepam redistributing to adipose tissue. The true $T_{1/2}$ is 36 hours, but the redistribution half-life is ≤ 1 hour

Benzodiazepine metabolism

- Benzodiazepines vary considerably in their metabolism and elimination rate.

Benzo	Primary metabolic pathway	Active metabolite	T1/2 of parent drug (hrs)	T1/2 of active metabolite (hrs)
Diazepam	Demethylation, hydroxylation, glucuronidation	**Desmethyldiazepam (DMD)**, oxazepam, temazepam	21-70	**DMD: 49-179** Oxazepam: 6-24 Temazepam: 8-24
Lorazepam	Glucuronidation	None	7-26	NA
Midazolam	Hydroxylation	1-hydroxymidazolam	2-6	3-7
Clonazepam	Nitroreduction, acetylation, hydroxylation	None	19-60	NA
Clorazepate	Decarboxylation	**DMD**, oxazepam	NA	**DMD: 20-160** Oxazepam: 6-24
Clobazam	Demethylation	N-desmethylclobazam	10-30	36-46

Benzodiazepine drug interactions

- Both pharmacokinetic and pharmacodynamic interactions occur
- Interactions depend on specific metabolic pathway
- Inhibition of major pathway may cause accumulation, but inhibition of minor pathway has limited effect
- Induction of major or minor pathways will reduce concentration
- Clinical effect of induction and inhibition also dependent on active metabolites and their metabolic pathways

Enzymes involved in metabolism of select ASMs

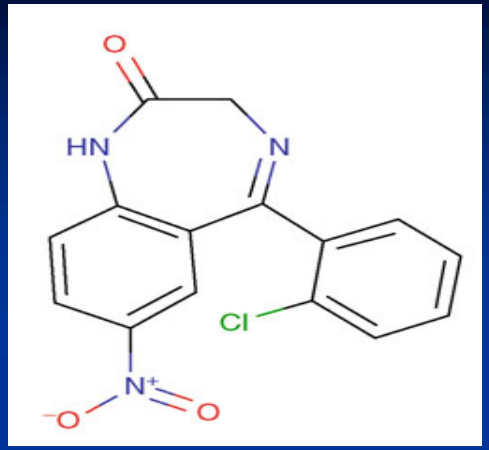
Enzyme	DZP	LZP	MDZ	CZP	CLZ	CLB
1A2						
2A6						
2B6	X					X
2C8						
2C9	X					
2C18						X
2C19	X				X*	X
2E1						
3A4	X		X	X	X*	X
3A5	X					
3A7						
4B1						
UGT		X				
NAT				X		

UGT= uridine diphosphate glucuronosyltransferase

NAT= N-acetyltransferase

*- applies to DMD

Clonazepam (CZP)



- Bioavailability>90%
- Tmax= 1-4 hours
- V_d= 3.0 L/Kg
- Protein binding: 85%
- Metabolism: hepatic
- $T_{1/2}$= 20-40 hours
- Minimal interactions- clearance increased by inducers

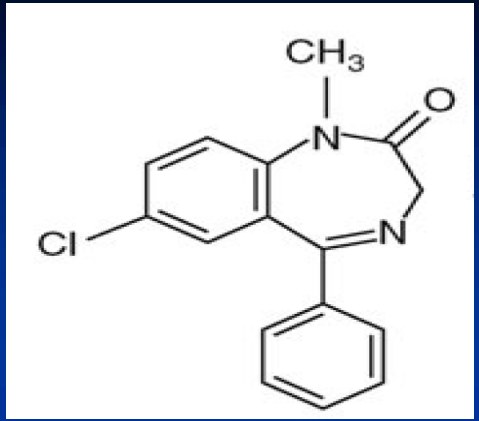
CZP- Adverse effects

- Drowsiness (tolerance to AEs develops)
- Nystagmus, incoordination, ataxia, dysarthria with higher doses
- Behavior disturbances more common in children- aggression, hyperactivity, paranoia
- Withdrawal seizures with abrupt discontinuation

CZP- Clinical use

- Used for long-term treatment as well as acute management- only oral form available in USA
  - Myoclonic seizures
  - Wide spectrum of efficacy against focal and generalized seizure types
- Dose: children- 0.01 to.0.02 mg/kg per day; adults up to 8 mg per day in two or three divided doses.
- Tolerance may develop to therapeutic effect

Diazepam (DZP)



- Bioavailability >90%
- Tmax: 1 hour
- V_d= 1-2 L/Kg
- Protein binding: 95%
- **$T_{1/2}$ = 36 hrs; initial $T_{1/2}$ = 1 hr**
- Liver metabolism- active metabolites with long $T_{1/2}$
- Induces CYP2B
- VPA increases free level through displacement from protein binding

DZP- Adverse effects

- Sedation
- Fatigue, amnesia, ataxia, falls in the elderly
- Blurred vision, diplopia
- Respiratory depression with IV use
- Withdrawal seizures after chronic use

DZP- Clinical use

- Available in oral tablet and liquid form, rectal gel, parenteral solution, nasal spray
- **Acute use for status epilepticus (but short duration of action requires additional agent), acute repetitive seizures (oral, rectal, or nasal)**
- **Usually not adequate for chronic use, except that courses can be used in some syndromes such as Landau-Kleffner syndrome and electrical status epilepticus during sleep (ESES)**

Diazepam nasal spray (VALTOCO)

- Intranasal preparation of diazepam formulated with Intravail A3 (n-dodecyl beta-D-maltoside [DDM]) and vitamin E to enhance solubility and absorption.
- Vitamin E increases the nonaqueous solubility of diazepam
- DDM is a nonionic surfactant that is used as an absorption enhancement agent to promote increased bioavailability of drugs across different types of mucosae

IN DZP Pharmacokinetics

Hogan et al, Epilepsia 2020

- Tmax 1.5 hours
- Bioavailability 97%
- T ½ ~49 hours
- 2-4 fold less intrasubject pharmacokinetic variability than rectal diazepam
- PK same interictally and ictally

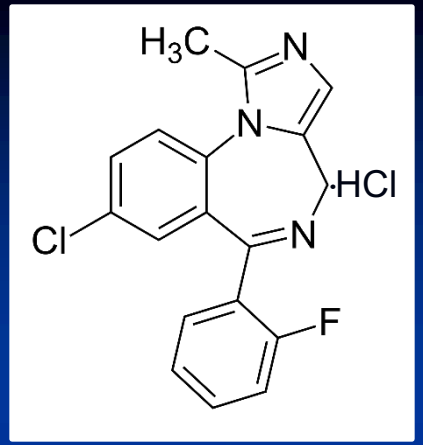
IN DZP FDA indication & dosing

- Approved in patients with epilepsy ≥6 years
- 5, 7.5, and 10 mg in 0.1 mL solution
- Age and weight-based dosing

6-11 years (0.3 mg/Kg)	≥12 years (0.2 mg/Kg)	Dose (mg)	Administration
10-18 Kg	14-27 Kg	5	5 mg in one nostril
19-37 Kg	28-50 Kg	10	10 mg in one nostril
38- 55 Kg	51-75 Kg	15	7.5 mg in each nostril
56-74 Kg	≥76 Kg	20	10 mg in each nostril

- May repeat in 4 hours- max 2 doses per cluster
- Max 1 episode per 5 days, 5 episodes per month

Midazolam (MDZ)



- Parenteral (IV, IM), IN spray, and buccal solution
- Parenteral midazolam as HCl for water solubility
- V_d= 1 to 3.1 L/kg
- 97% protein-bound
- Hepatic metabolism by CYP 3A4 to hydroxylated metabolites (including active 1-hydroxy-midazolam) that are conjugated and excreted in the urine.
- T ½= 1.8 to 6.4 hours (mean ~3 h)
- Linear kinetics up to 0.3 mg/kg, nonlinear at ≥ 0.45 mg/kg
- IM injection Tmax: 30 min; onset of sedative effects 15 min in adults, 5 min in children- Cmax half of IV

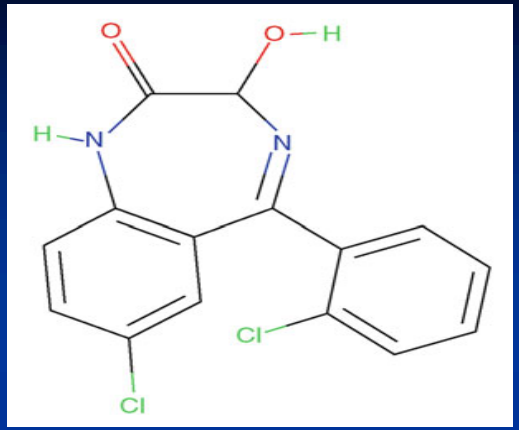
Intranasal Midazolam (Nayzilam)

- Midazolam (MDZ) formulation, optimized for delivery, including appropriate volume for nasal route of administration
- Median Tmax 17 min (7.8-28)
- Cmax and AUC proportional to dose
- Absolute bioavailability 44%
- 97% bound to plasma proteins
- Primarily metabolized by liver and intestinal CYP3A4 to active metabolite, 1-hydroxy midazolam. T1/2= 2.1-6.2 & 2.7-7.2 hrs

MDZ nasal spray- indication and dosing

- Approved in patients ≥ 12 years
- 5 mg in one nostril
- May repeat in the other nostril after 10 minutes
- Max 2 doses per cluster
- Max one episode every 3 days; 5 episodes per month
- Avoid using with opioids

Lorazepam (LZP)



- Oral bioavailability >90%
- Tmax: 1.5-2 hours
- V_d= 1 L/Kg
- Protein binding: 90%
- $T_{1/2}$ = 15 hrs
- Metabolized in the liver through glucuronidation and excreted by the kidneys
- **Clearance reduced by VPA and other inhibitors**

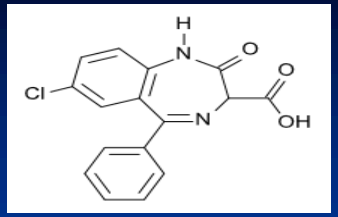
LZP- Adverse effects

- Sedation, dizziness, vertigo, weakness, unsteadiness, dysarthria
- Disorientation, depression, headache, agitation or restlessness, emotional disturbances, hallucinations, delirium
- Impaired psychomotor performance, anterograde amnesia
- Mild respiratory depression with IV use
- Withdrawal seizures from sudden discontinuation

LZP- Clinical use

- Available in oral and parenteral forms
- Can be given sublingually
- Usually not appropriate for chronic use
- **Status epilepticus (longer duration of action than DZP despite shorter half-life**, and less respiratory depression makes it preferable)
- Acute repetitive seizures

Clorazepate (CLZ)



- Bioavailability 100%
- Tmax= 0.5-2 hours
- Protein binding: 96%
- Prodrug, rapidly decarboxylated in the stomach to form the active desmethyldiazepam (DMD- also called nordiazepam) with an average $T_{1/2}$ of ~ 2 days

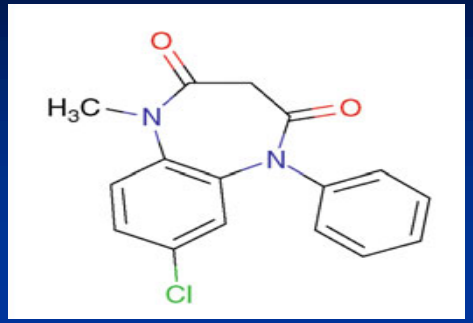
CLZ- Adverse effects

- Drowsiness
- Dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, mental confusion.
- Dependence
- Withdrawal symptoms with discontinuation

CLZ- Clinical use

- FDA approved for management of anxiety disorders and as adjunctive therapy in the management of partial seizures.
- Available in immediate and extended release preparations

Clobazam (CLB)



- **Only 1,5-benzodiazepine ASM**
- Bioavailability >90%
- Tmax= 1-4 hours
- Protein binding: 85%
- $T_{1/2}$= 10-30 hours
- Metabolized in the liver to the active N-desmethylclobazam (T1/2= 42 hrs)
- N-desmethylclobazam is metabolized by CYP2C19- accumulates in presence of inhibitors (such as cannabidiol, felbamate, cenobamate, stiripentol)

CLB has higher selectivity for α2-containing $GABA_A$ receptors 1,4-benzodiazepines have stronger sedative effect by way of interaction with α1 subunits

	GABAA Receptor subtype	
	α1	α2
Analgesia		XX
Anxiolysis		XX
Muscle relaxation		XX
Anti-convulsant	XX	XX
Sedation	XX	
Cognitive impairment	XX	?
Addiction	XX	X

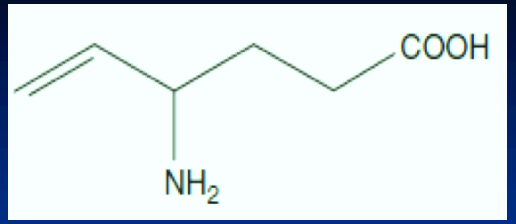
CLB- Adverse effects

- **Less sedation than with 1,4-benzodiazepines**
- Drowsiness, fatigue, ataxia, dizziness, memory disturbance, aggressiveness
- Tolerance may develop, but less than with 1,4-benzodiazepines
- Seizures may occur with acute withdrawal

CLB- Clinical use

- Available in tablets and syrup
- Widely used for long-term treatment of epilepsy
- FDA indicated for Lennox-Gastaut syndrome (adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients ≥2 years)
- Broad spectrum of efficacy, as with other benzodiazepines

Vigabatrin (VGB)



- Initially licensed in Europe in 1989. First approved in the USA in 2009
- MOA: irreversible inhibition of GABA transaminase (designer drug)

VGB- Absorption, distribution

- Oral bioavailability nearly complete
- Tmax = 1 hour for children and adults, 2.5 hours for infants
- Protein binding: none
- V_d = ~0.8 L/Kg

VGB- Metabolism, elimination

- Not significantly metabolized
- Elimination by excretion in urine, unchanged
- $T_{1/2}$ = 10.5 hours in young adults, 5–6 hours in infants.

VGB- Interactions

- VGB is a weak inducer of CYP2C9
- PHT levels decrease ~20% with addition of VGB

VGB- Adverse effects

- Sedation, fatigue, dizziness, ataxia
- Irritability, behavioral changes, psychosis, depression
- Weight gain
- **Bilateral concentric visual field constriction,** progressive and permanent (up to 30%- risk increases with dose and duration of Rx)
- **MRI changes in infants-** increased T2 and restricted diffusion in deep white matter, basal ganglia, thalamus, and corpus callosum (asymptomatic and reversible)

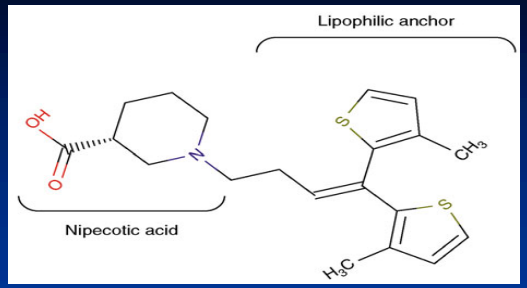
VGB- Efficacy/ Clinical indications

- Effective against focal seizures; may worsen absence and myoclonic seizures in IGE
- FDA indications
  - "Adjunctive therapy for adults and pediatric patients ≥10 years with refractory complex partial seizures who have responded inadequately to several alternative treatments"
  - "Monotherapy in infants with infantile spasms 1 m to 2 yrs of age, for whom the potential benefit outweighs the potential risk of vision loss"

VGB- Monitoring

- **Periodic visual assessment is recommended (at baseline and every 3 months)**
  - perimetry in cooperative adult and pediatric patients.
- Additional optional testing may include electroretinography (ERG) and retinal imaging with optical coherence tomography (OCT)
- Treatment should not be continued if therapeutic benefit is insufficient

Tiagabine (TGB)



- First approved in the USA in 1997.
- MOA: inhibition of GABA uptake at the synapse.
- Requires slow titration

TGB- Absorption, distribution

- Oral bioavailability: 90-95%
- Tmax = 1-1.5 hours
- **Protein binding: 96%**
- V_d = ~1 L/Kg

TGB- Elimination

- Extensively metabolized in the liver; mainly by cytochrome P450 enzyme CYP3A
- 63% excreted in feces, 25% in urine (<2% unchanged)
- $T_{1/2}$ = **7–9 h in monotherapy** (normal volunteers); 2-5 hours with enzyme inducers (epilepsy patients), requiring tid dosing

TGB- Interactions

- TGB does not affect other medications.
- Even though TGB is highly protein bound, levels are low and this is not a source of interaction.
- **TGB metabolism is accelerated by enzyme-inducing drugs.**

TGB- Adverse effects

- Most commonly reported AEs: dizziness, asthenia, nervousness, tremor, depression, emotional lability.
- AEs more common during titration- requires slow titration and tid dosing.
- **Nonconvulsive status epilepticus/ encephalopathy-** dose dependent. **May occur in the absence of epilepsy.**

TGB- Efficacy/ clinical indication

- Effective against focal seizures
- Not effective against, and may exacerbate generalized absence or myoclonic seizures
- FDA approved for adjunctive therapy in adults and children ≥12 years in the treatment of partial seizures

Stiripentol (STP)

- Approved by FDA in 2018 for the treatment of seizures associated with Dravet syndrome in patients ≥2 years also taking clobazam.
- Mechanism of action may involve both direct interaction with the $GABA_A$ receptor (allosteric modulation) and inhibition of CYP enzyme activity resulting in increased concentration of clobazam and its active metabolite.

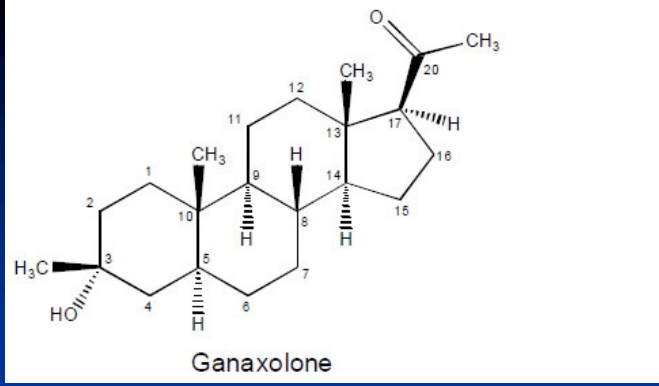
STP- Absorption, distribution, elimination, interactions

- Oral bioavailability: 90-95%
- Tmax = 2-3 hours
- **Protein binding: 99%**
- Metabolism: through CYP1A2, CYP2C19, CYP3A4
- T1/2= 4.5-13 hours, increasing with increased dose ≥ 500 mg, and with weight in children with Dravet syndrome
- Inhibits CYP enzymes, particularly CYP2C9 and CYP2C19- causes elevation of N-desmethylclobazam, active metabolite of clobazam, and valproate

STP- clinical indication, adverse effects

- Currently indicated only for the adjunctive treatment of patients with Dravet syndrome also taking clobazam
- Recommended dose is 50 mg/kg/d administered in 2 or 3 divided doses, not to exceed 3000 mg/d.
- Requires reduction of concomitant clobazam, valproate
- Most common adverse experiences occurring more frequently than with placebo are somnolence, anorexia, nausea, and weight loss.

Ganaxolone (GNX)



Ganaxolone

- Neuroactive steroid
- Positive allosteric modulator of GABA-A receptor that targets a unique binding site distinct from benzodiazepines or barbiturates

GNX- absorption, distribution, metabolism

- Oral bioavailability
- Vd= 11.9L/Kg
- Tmax 2-3 hours
- Protein binding: 50%
- Cmax and AUC increased by 3-and 2-fold, when administered with a high-fat meal vs fasted conditions.
- Protein binding: ~ 99%
- Metabolized by CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6
- T1/2= ~34 hours.
- Not an inducer or inhibitor
- Clearance increased by enzyme inducers

GNX- Adverse effects

Adverse Reactions	GNX (N=50) %	Placebo (N=51) %
Somnolence	38	20
Pyrexia	18	8
Upper respiratory tract infection	10	6
Sedation	6	4
Salivary Hypersecretion	6	2
Seasonal allergy	6	0
Bronchitis	4	0
Influenza	4	2
Gait disturbance	4	2
Nasal congestion	4	2

GNX- Clinical indication

- Treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older

GNX- Dosage and administration

- TID with food
- Dosage for patients weighing 28 kg or less:
  - starting dosage: 6 mg/kg tid (18 mg/kg/day)
  - increase by 5 mg/Kg tid every week
  - maximum dosage: 21 mg/kg tid (63 mg/kg/daily)
- Dosage for patients weighing over 28 kg:
  - starting dosage: 150 mg tid (450 mg daily)
  - increase by 150 mg td every week
  - maximum dosage: 600 mg tid (1800 mg daily)