Cleveland Clinic Children's

Epilepsy Center

ASD II: Evidence Based use of ASD
First Generation AEDs, and Drug Interactions

Ahsan *Moosa* Naduvil Valappil, MD

Staff, Pediatric Epilepsy, Epilepsy Center

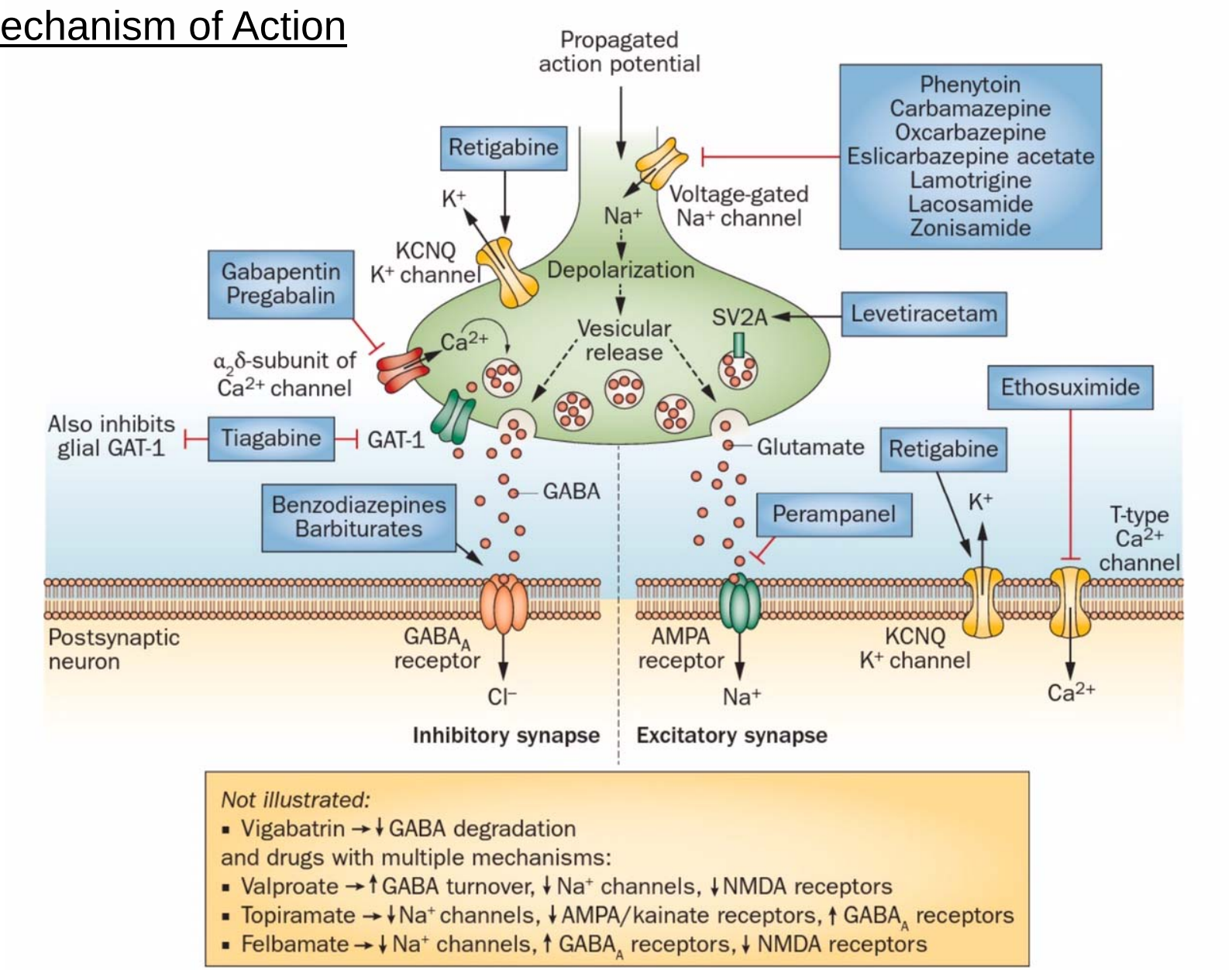
naduvia@ccf.org

@AMoosaMD

Outline

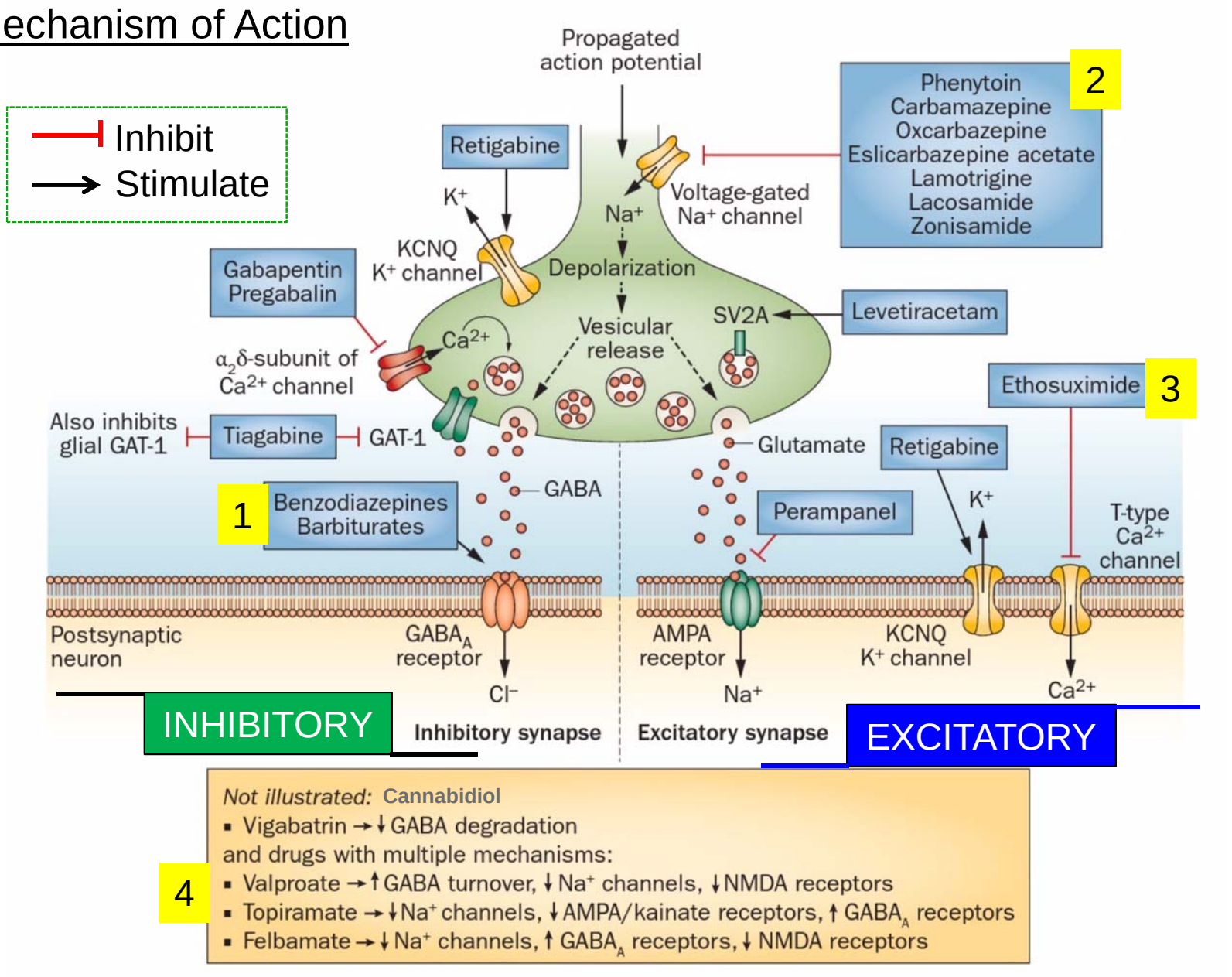
- Overview of mechanism of action of anti-seizure medications
- Discuss few first generation ASDs:
  - Phenobarbital, Phenytoin, Carbamazepine, Ethosuximide, Valproic acid
- Discuss mechanism of Drug interactions in epilepsy practice

Mechanism of Action



Nature Reviews I Neurology Dec 2012 8:661
Modified from Bailer M, White HS Nature Rev Drug Discov 2010

Mechanism of Action



Nature Reviews I Neurology Dec 2012 8:661

Modified from Bailer M, White HS Nature Rev Drug Discov 2010

Phenobarbital *since 1912*

- **GABA-ergic**
  - **Enhances post synaptic $GABA_A$ mediated Cl^- channel -- > hyperpolarization & inhibition**
- **Minor effect on sodium and K conductance, calcium influx**
- **Broad spectrum**
- **Low cost**

Primidone

- Pro-drug: Phenobarbital and phenylethylmalonamide
- Poorly soluble
- Transient debilitating sedation, ataxia- more than PHB. Slow titration recommended
- Other interactions similar to PHB

Adverse effects

- Hyperactivity in children
- Reduced bone density
- Connective tissue disorders
  - Dupuytren’s contracture
  - Shoulder peri-arthritis.
  - Plantar fibromatosis
- Not a preferred AED in developed countries

Phenytoin *since 1938*

- Blocks voltage gated sodium channels
  - Slow recovery and limits repetitive firing
- Focal seizures and GTCS
- Not effective for absence seizures, spasms, myoclonic seizures
- Worsening: Dravet syndrome (SCN1A mutation) & Unvericht-Lundborg syndrome

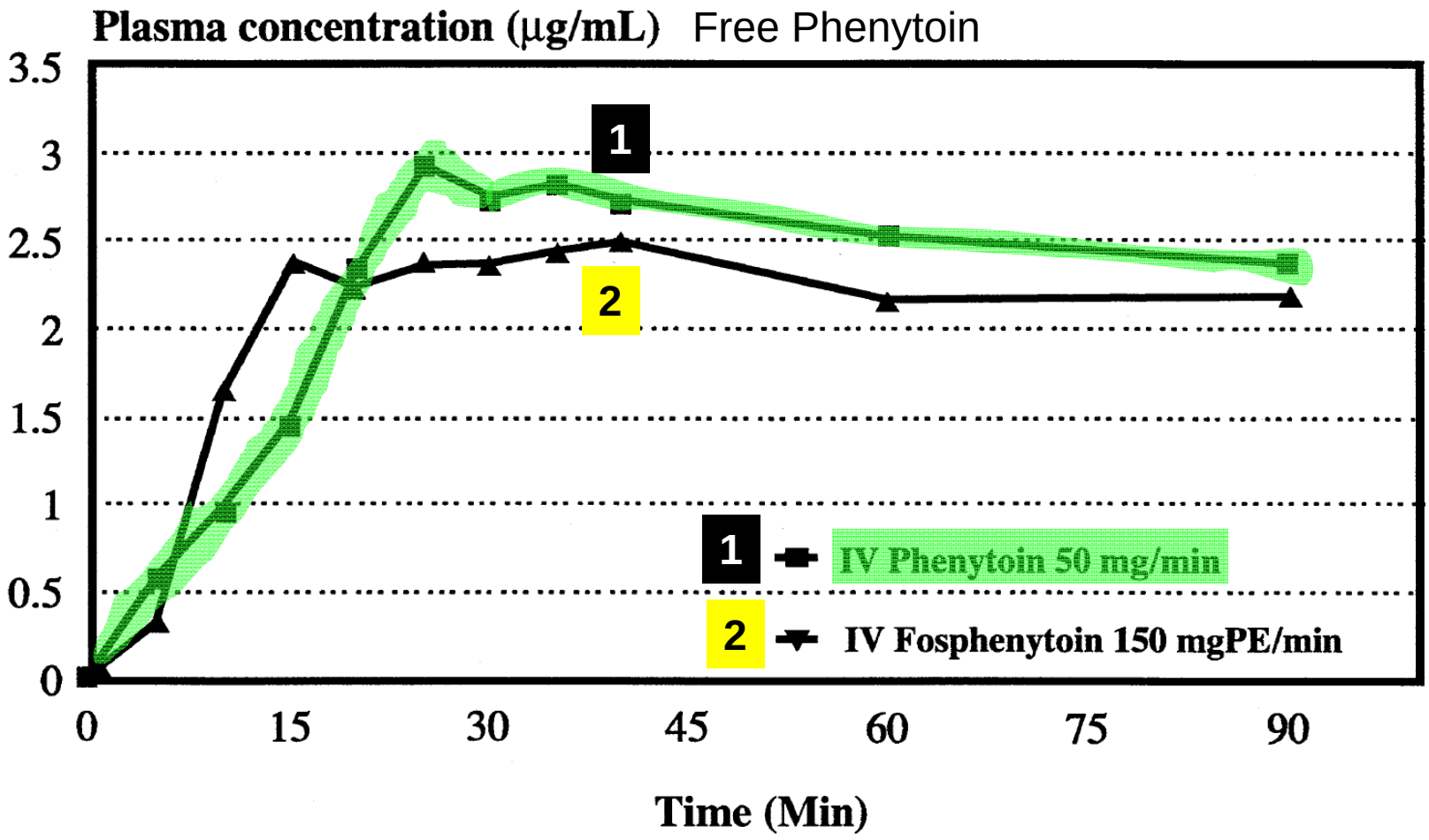
✓ Effective in certain patients with SCN8A, SCN2A and KCNQ2 (gain of function mutations)

Adverse effects

- Gingival hyperplasia (~40%)
- Reduced bone density- vitamin D metabolism
- Lymphadenopathy
- Hyper-trichosis
- Cross reactivity- allergy between CBZ
  - HLA-B 1052
- Fetal hydantoin syndrome
- Purple glove syndrome with extravasation

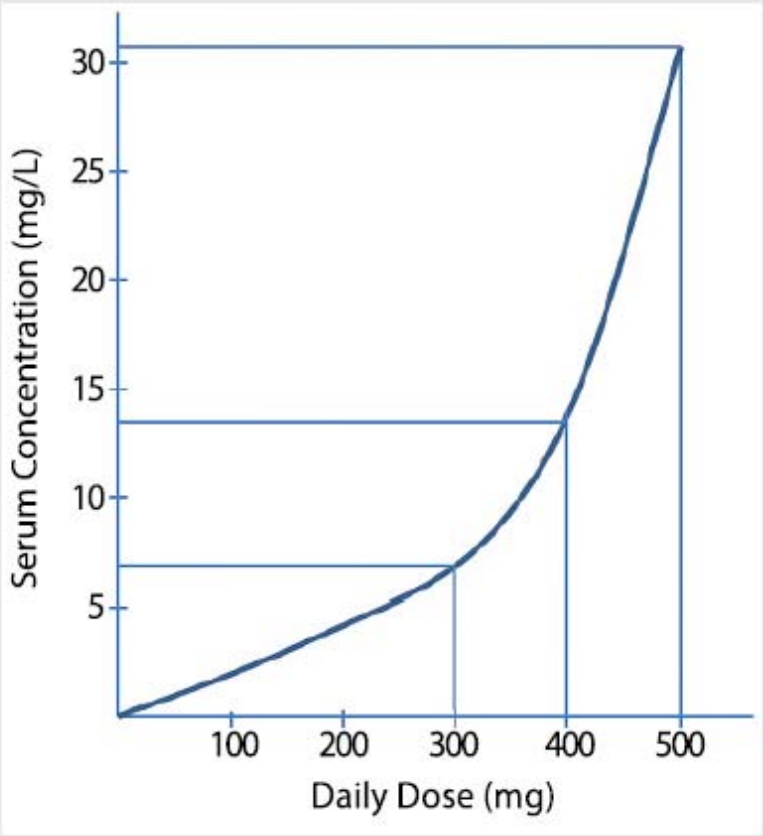
Fosphenytoin (fosPHT)

- Prodrug
  - 1.5 mg fosPHT yields 1 mg PHT (100 mg PE = 100 mg phenytoin)
- Less risk for cardiovascular complication
- Less risk for phlebitis/purple glove
- Can be given i.m.
- Rate of administration in emergencies
  - FosPHT @100 to 150 PE/min (vs Phenytoin @50 mg/min)



Modified from
Eldon M et al. Can J Neurol Sci, 1993

Phenytoin:
Non-linear Kinetics
Zero order kinetics



First order: A fixed proportion of drug eliminated
Zero order: A fixed amount of drug eliminated
In higher doses, lower increments needed to avoid toxicity

Ref: Abou-Khalil. Continuum 2016; 22:132-156.

Carbamazepine *since 1960s*

- Blocks voltage gated sodium channels
  - Slow recovery (increases refractory period) and limits repetitive firing
- Also blocks L-type calcium channels
- Focal seizures and GTCS
- Not effective for absence seizures, spasms, myoclonic seizures

Auto-induction

- CBZ metabolized by CYP3A4 isoenzyme in cytochrome oxidase family
- CBZ also induces CYP3A4 hepatic synthesis
- Enhances its own metabolism = auto-induction
- Auto-induction occurs 1-3 weeks later
  - Levels may be higher in lower doses –(early) and drop later with higher doses
- Toxicity if titrated too fast

Adverse effects

- CBZ -epoxide responsible for many adverse effects (an active metabolite with anticonvulsant effect)
- Transient leukopenia in 1-20% in 1st 3 months
- Propensity to toxicity with CYP3A4 inhibitors
  - Grapefruit juice
  - Erythromycin, Clarithromycin
  - Ketoconazole, Metronidazone, Indinavir
  - Ca channel blockers
- Hyponatremia –less common in children; higher in older age
- Stevens-Johnson Syndrome- higher risk with Asian ancestry.

Pharmacogenomics

- Risk for Steven Johnson Syndrome in Asians **x 10** compared to Caucasians
- **HLA-B *1502** allele increases the risk
- **FDA recommends** genetic testing prior to initiating therapy with CBZ in patients with Asian ancestry

TABLE 1. *HLA-B*15:02* FREQUENCY[1]	
Country/ Region/Ethnicity	***HLA-B*15:02*** **Allele Frequency**
China	1-12%
Singapore	10-12%
Hong Kong	10-12%
Malaysia	6-8%
Thailand	6-8%
India	2-6%
Korea	0.5%
Japan	0.1%
African populations	0-0.02%
European populations	0-0.02%

McCormack et al. *NEJM* 2011; 364:1134-43.
Leckband, S. G. *et al. Clin Pharmacol Ther* **94**, 324-328

Oxcarbazepine

- 10,11-dihydro-10-oxo-carbamazepine
- Prodrug
  - Monohydroxyl derivative (active compound)
- Block Na channel and N-type Ca channels

✓ No auto-induction

✓ Not prone to CYP3A4 drug interactions

- Hyponatremia:
  - 7.3% in age >65 yrs; 3.4% age 18-64 yrs

Ethosuximide *since 1958*

- Blocks T-type calcium channels in thalamus
  - Other drugs on same channel
  - Other Ca channels
- Narrow spectrum- almost exclusively used in absence epilepsy
  - Sometimes used in ESES (‘spike-wave complexes’)
- Hepatic metabolism- prone to enzyme inducer interactions.
- 90% bioavailable; t ½=30-60 hrs; protein binding <10%

Adverse Effects

- GI symptoms: Nausea, abdominal pain, emesis, diarrhea
  - Divided doses, after food, acid blockers help
- Headaches in some patients
- Irritability, depression, hallucination occasionally.
- Neutropenia (check counts during infection?), transaminitis, rash, SJS

✓ Lupus like syndrome

Valproic Acid *since **1978***

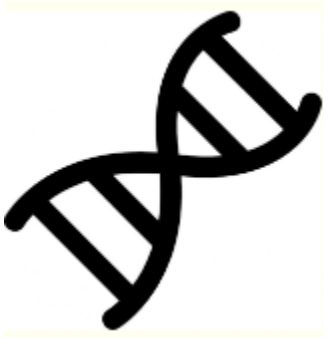
- **Blocks voltage gated sodium channels**
- **Inhibits ‘T’ type calcium Channel (same as ETX)**
- **Increase GABA**
  - Inhibits GABA transaminase
  - Inhibits succinic semialdehyde dehydrogenase
  - Decrease clearance through transporter down regulation
  - Induce GABA synthetic enzyme
- **Broad spectrum**

Adverse effects

- Thrombocytopenia (dose dependent frequently)
- Platelet dysfunction, Pancreatitis
- Weight gain, hair loss (curly regrowth), polycystic disease/ menstrual irregularities
- Teratogenic, increased risk (~30%) for autism/ low IQ disabilities in children exposed in utero
- Hyperammonemia (concomitant therapy with Topiramate may increase)

Fatal Liver toxicity Rare in Adults

- The risk for fatal hepatotoxicity in patients receiving VPA polytherapy is approximately
  - 1:600 at younger than 3 years of age,
  - 1:8,000 from 3 to 10 years,
  - 1:10,000 from 11 to 20 years,
  - 1:31,000 from 21 to 40 years, and
  - 1:107,000 at older than 41 years of age.
- Carnitine treatment improved survival in liver failure related to VPA



Pharmacogenomics

- Patients with certain **POLG1** mutations- high risk for VPA liver failure; usually same mutations that cause neurological disease.
- Liver failure also reported with other mutations such as TWINKLE gene
- No specific recommendation for testing; in children with unclear etiology for epilepsy, testing is preferred by many clinicians.
- Caution:
  - In mitochondrial disorders
  - Young children with seizures/ encephalopathy of unknown cause

Isohanni, et al. Neurology 2011; 76:811-15.
Stewart JD et al. Hepatology 2010; 52:1791-6

Benzodiazepines

- GABA ergic
- Increases GABA mediated chloride channel opening
- Drugs
  - Chronic: Clobazam, Clorazepate, Clonazepam
  - Acute: Diazepam, Lorazepam
  - Clobazam- FDA approved for LGS
  - Diazepam- ESES/LKS
- Kinetics: redistribution to adipose tissue (particularly with Diazepam)- 2 compartment model.
- Metabolized by CYP3A4 and CYP2C19

Rapid Redistribution

- After IV Diazepam
  - Elimination ½ life: 20-50 hrs
  - Duration of action is only 20-30 min (Peak brain concentration for 20-30 min)
- After IV Lorazepam
  - Elimination ½ life 14 hrs
  - Duration of action ~ 6 hrs
  - Less respiratory depression with LZM

Greenfield & Co. Wyllie's Treatment of Epilepsy; 6th edition, chapter 55

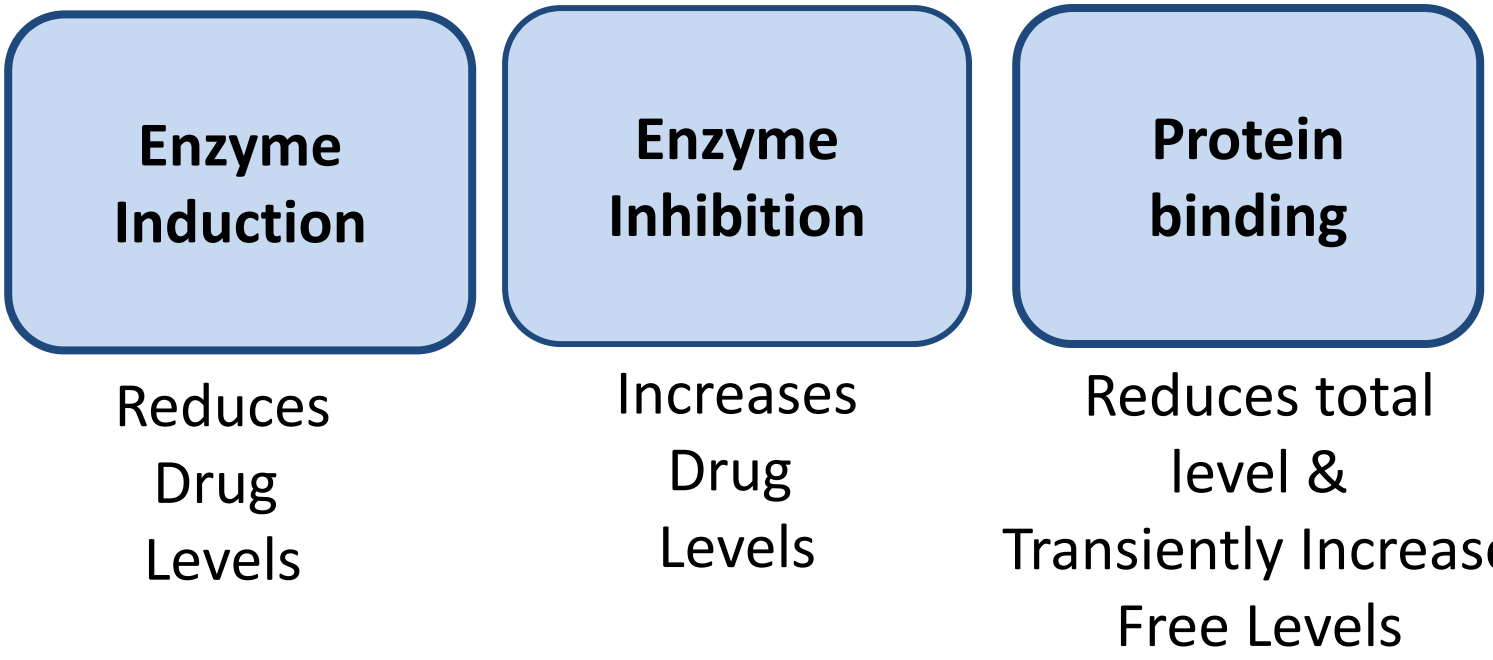
Part 2

1st Gen AEDs

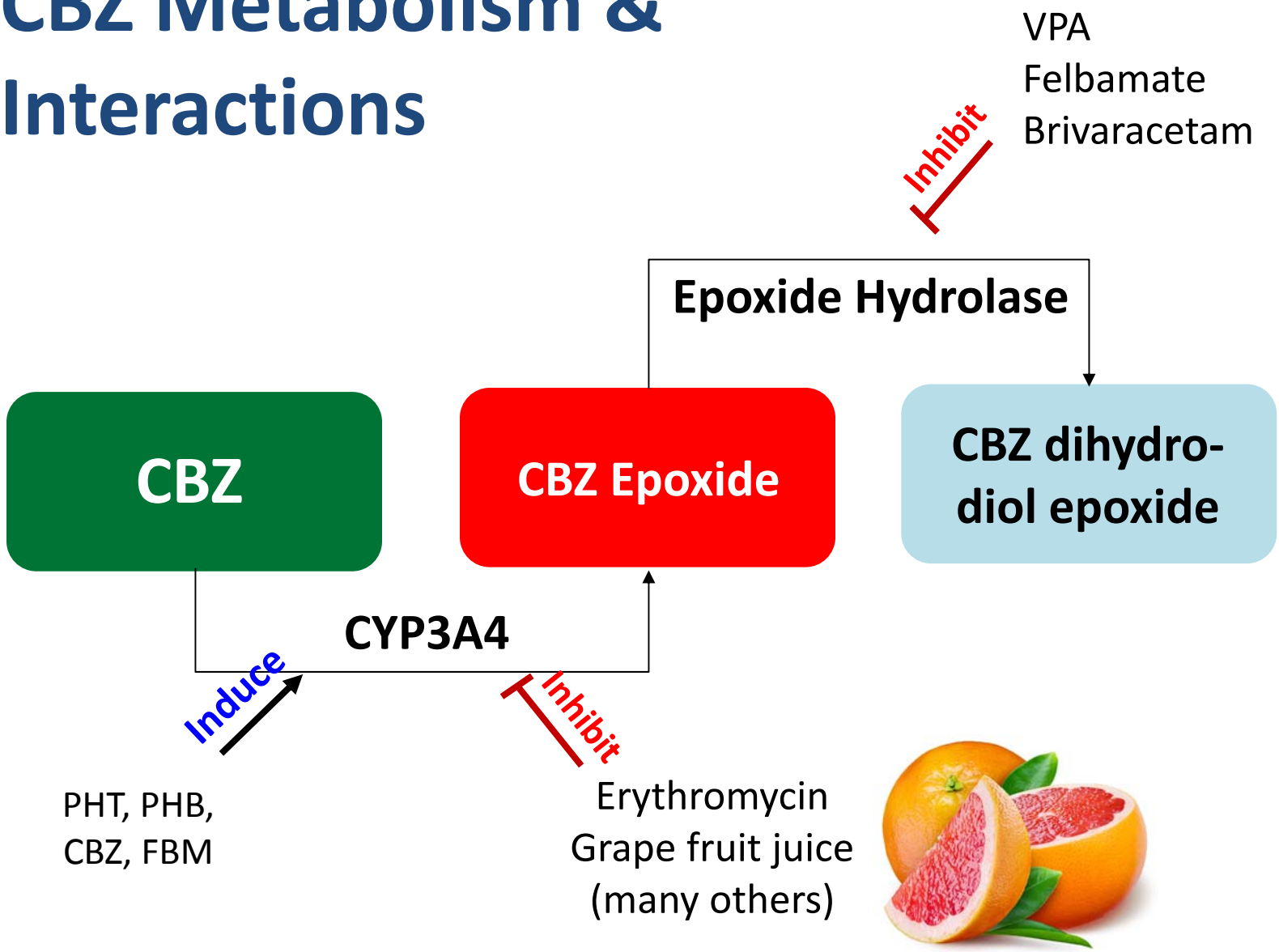
PHT, CBZ, OXC
PHB, Benzos
ETX, VPA

Drug Interactions

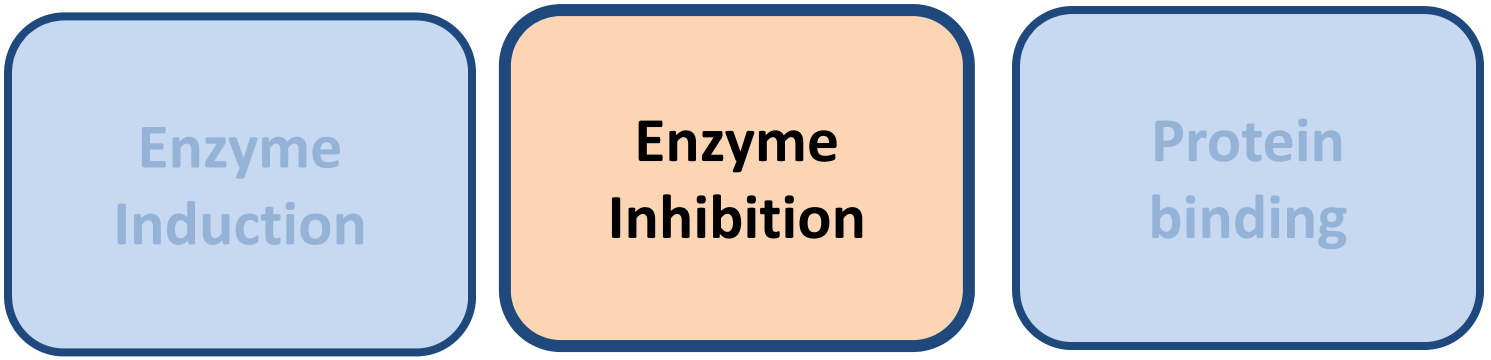
Pharmacokinetic- Drug Interactions



CBZ Metabolism & Interactions



Drug Interaction



Enzyme Inhibition

Often affects drug levels immediately (hours in VPA)

Often more dramatic/clinical significant interactions- because of acute toxicity

Enzyme inhibition is often selective (narrow spectrum of enzymes)

Enzyme Inhibition
Some examples

1. Valproate increase LTG (titration schedules different based on co-medication)
2. Valproate increases RUF (less dramatic than LTG)
3. VPA and Brivaracetam increases CBZ epoxide (by inhibiting EH)
4. Felbamate increase PHT (also OXC, TPM)
5. Carbamazepine increased by CYP3A4 inhibitors* (e.g., erythromycin)

* Several CYP3A4 inhibitors in ID world

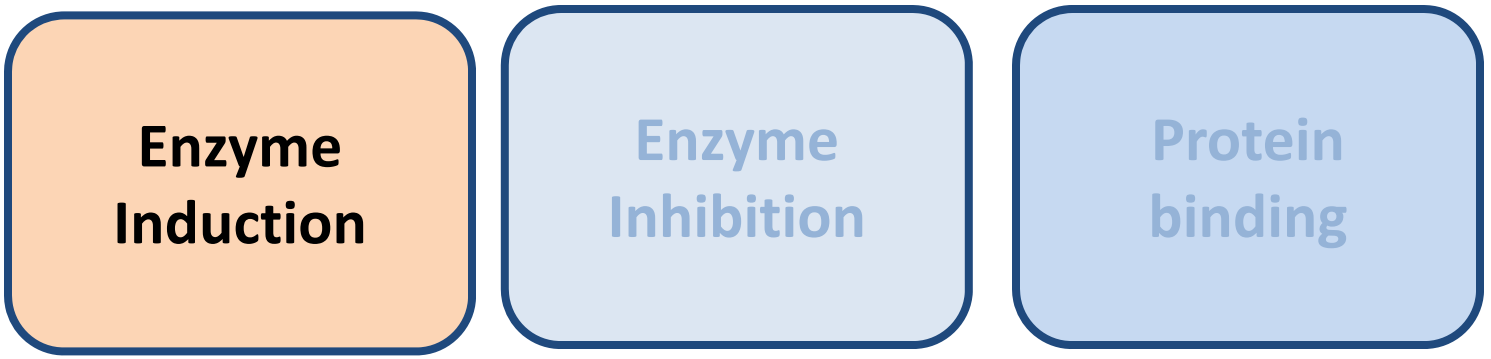
A!

ARS

- ALL of the following cause lower levels of Valproate EXCEPT
  1. Enzymatic induction from phenytoin
  2. Enzymatic induction from Pentobarbital
  3. Co-administration of Meropenem
  4. Co-administration of Topiramate

Ref: Polard & Delanty. Continuum Life Long Learning Neurol 2007; 13:91-105
Ref: Wu et al. Ther Drug Monit 2016;38:587-592 (Valproate & Carbapenem)

Drug Interaction



Enzyme Induction

Often affects drug levels in 1-3 weeks

May be missed unless AED levels checked (or seizures recur)

Enzyme induction is often broad

After stopping the inducer, take 1-3 weeks for induction to subside.

Valproate & Carbapenem Antibiotics

- Valproate levels dramatically fall when patients received Carbapenems (Imipenem, Meropenem, Ertapenem)
- Inhibition of deconjugation enzymes- a putative valproic acid glucuronide deconjugation enzyme (VPAGase), responsible for the deconjugation of VPA-glucuronide.
- Dose adjustments –often does not work
- Levels rebound 1 week after stopping the penems.

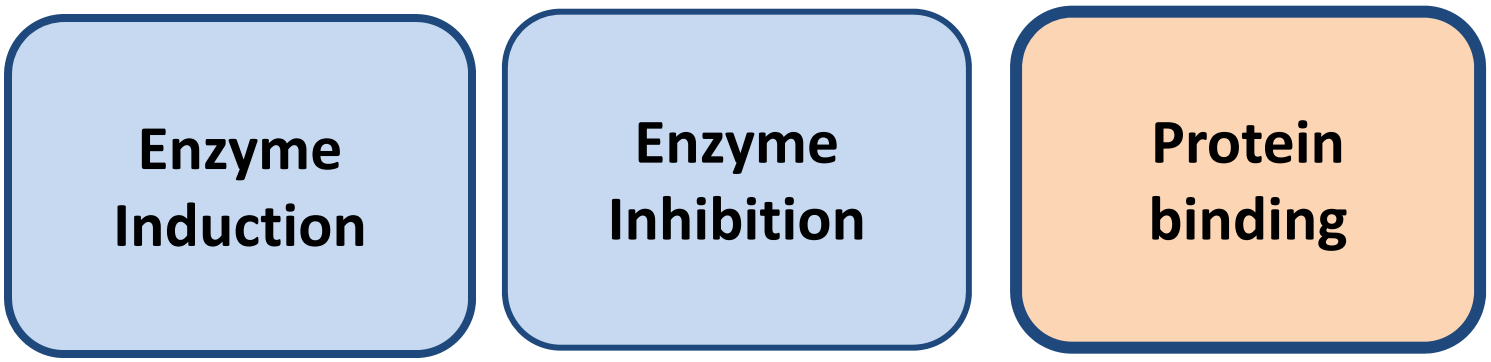
Enzymes & AEDs

INDUCERS	INHBITORS	MIXED
Phenobarbital	Valproate	Oxcarbazepine
Phenytoin	Oxcarbazepine	Topiramate
Carbamazepine	Topiramate	Felbamate
Primidone	Felbamate	
Ethosuximide (weak)	BRV, CBD, CLB, ESL	
	Cenobamate	

Oxcarbazepine
Topiramate
Perampanel

Not a complete list
For newer AEDs, data incomplete

Drug Interaction



Others: Absorption related & pharmacodynamic

Protein Binding

- Protein binding causes clinically relevant interactions (displacing free drug levels) if the protein binding is high – i.e. in 90s
- Other factors influence as well. e.g. hepatic extraction ratio, route of administration
- High protein bound
  - Phenytoin
  - Valproate
  - Diazepam
  - Clorazepate
  - Lorazepam
  - Tiagabine
  - Peramapanel

  } Clinical relevant interactions
- Transient issues; usually no major long term concerns.

NEWER ASDs

DRUG	EFFECT	ENZYMES INVOLVED	Some drug interactions
Perampanel (PER)	Induce	CYP3A4	BC pills CBZ, OXC,,PHT (not PB) increase PER metabolism
Eslicarbazepine (ESL)	Inhibits	CYP2C19	EIAEDs induce ESL metabolism ESL increase PHT level
Rufinamide (RUF)	Induces	CYP3A4	EIAEDs induce RUF metabolism VPA Increase RUF level
Vigabatrin (VGB)	Induces	CYP2C19	Reduced PHT Increase CZP level by 30%
Brivaracetam (BRV)	Inhibits	Epoxide hydrolase	Increase CBZ-epoxide 100% Increase PHT 20% EIAEDs decrease BRV
Cannabidiol (CBD)	Inhibits	CYP2C19 2C9,UGT	Increase N-desmethyl CLB x 3 CBD prone to CYP3A4 altering drugs
Clobazam (CLB)	Inhibits	CYP2D6	Dextromethorphan increase (2D6) CYP2C19 Inhibitors increase CLB
Cenobamate	Inhibits	CYP2C19	Increase phenobarb and phenytoin levels

Key Points on Drug Interactions

- Drug interactions are frequent when using 1st generation AEDs
- Enzyme inhibition interactions are often acute and dramatic (toxicity effect)
- Enzyme induction is often delayed and may go unrecognized until seizure recurrence – monitor AED levels

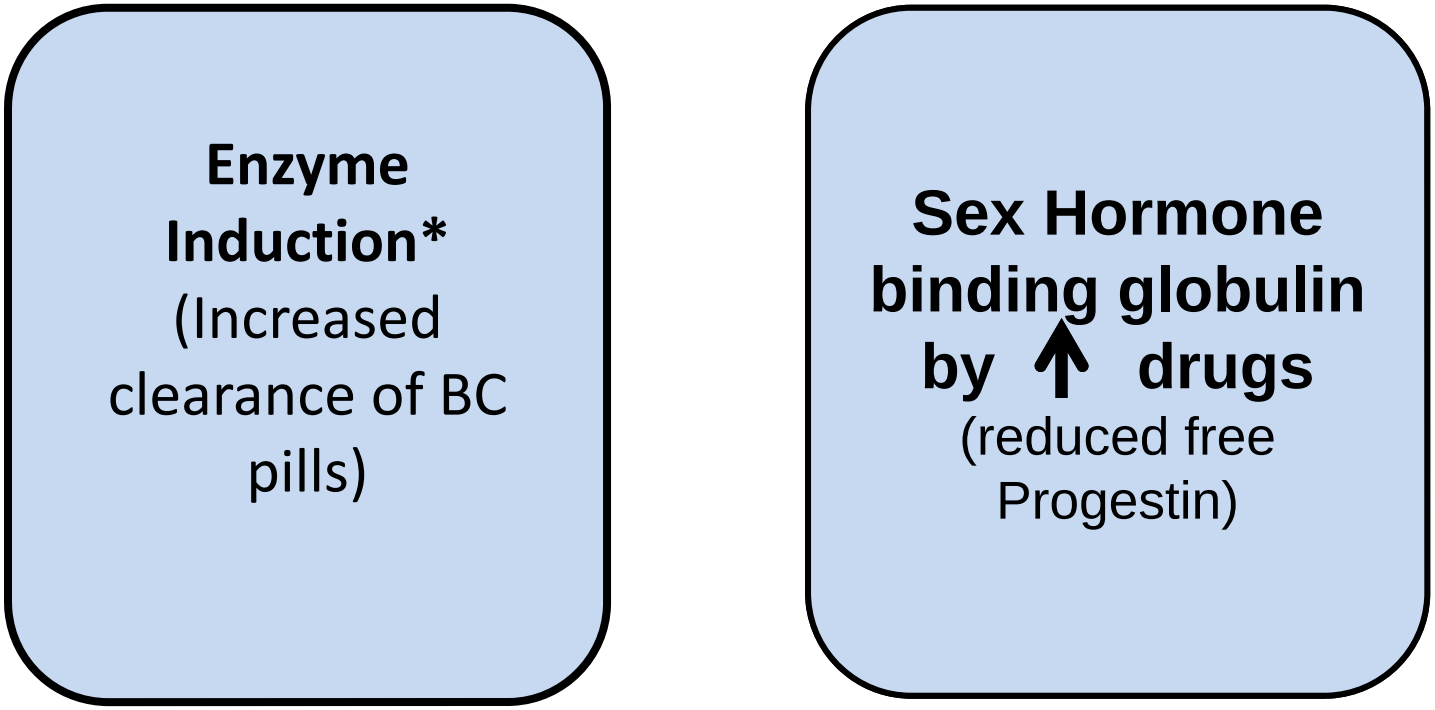
Cleveland Clinic

Every life deserves world class care.

Good Luck

Additional Material for Review

Drug Interaction: BC Pills



***CYP3A4 enzyme group**

PHB, PHT
CBZ, OXZ

Antiepileptic Drugs That Induce Metabolism of One Component of Contraceptive Pill

- Carbamazepine
- Felbamate
- Lamotrigine (Higher doses)
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Primidone
- Topiramate (≥200 mg/d)
- Perampanel* (>8 mg)

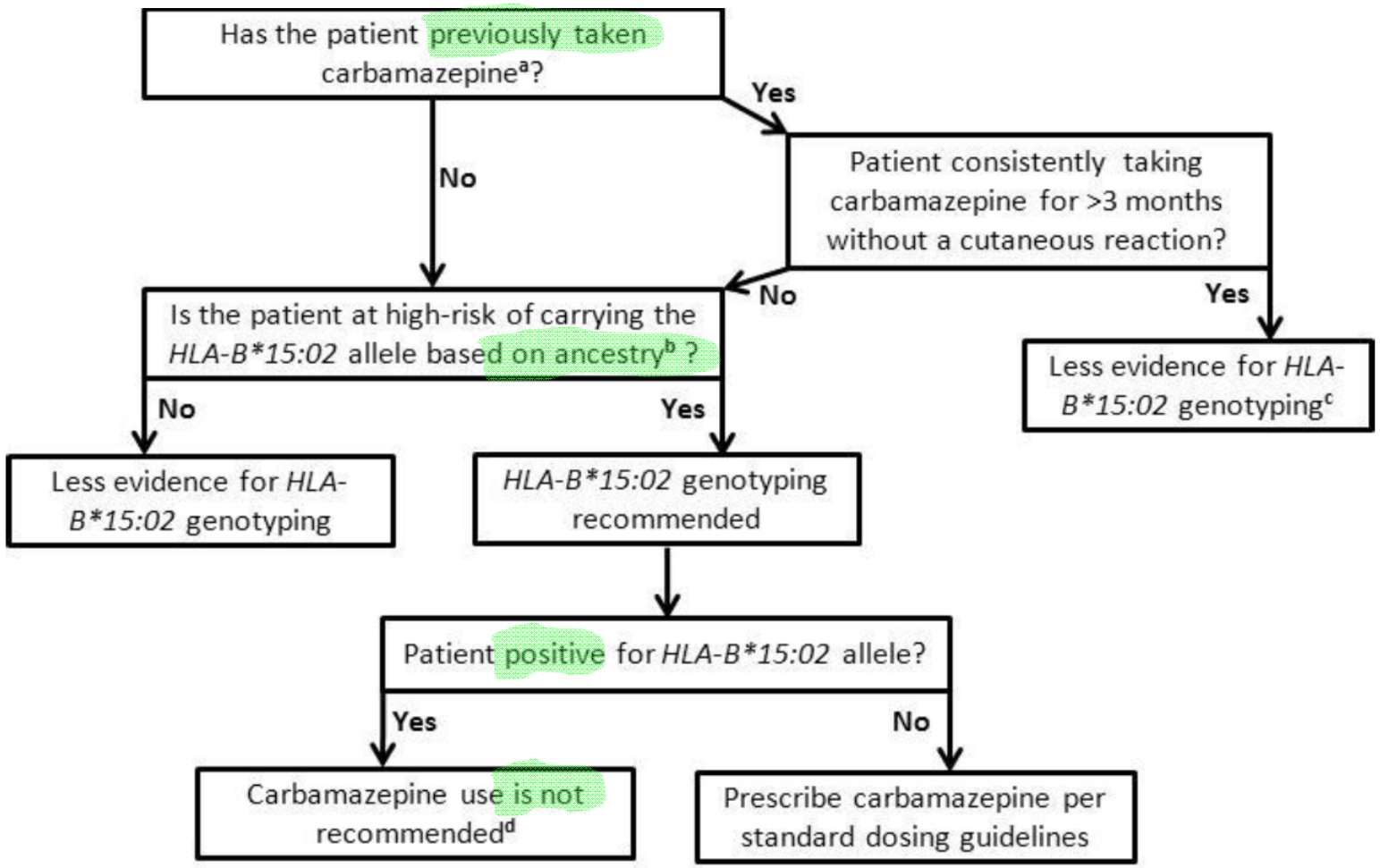
* Affects progesterone component

BC Options

Higher dose
Depot Progesterone
IUD
Barrier methods
Double method

Modified from: Continuum Lifelong Learning Neurol 2007;13(4):91-105

HLA testing for CBZ Initiation



Cleveland Clinic Formulary

Pharmacokinetics

Drug	Bio-availability	Half life	Protein Binding	Vd L/kg	Metabolism	Unique features
PHB	**80-90%**	**80-100 hrs 100-150 NB**	**45% (20-60)**	**0.6**	**75% liver 25% renal**	**Inducer of P450**
Primidone	**>90%**	**10-15 hrs**	**<10%**	**0.54-0.86**	**25% converted to PHB**	**Inducer of P450**
CBZ	**70-80%**	**10-25 hrs**	**75% (67-81)**	**0.8-2**	**90% hepatic**	**Auto-induction CBZ-CBZ epoxide- CBZ dihydridiol epoxide**
OXC	**>90%**	**1-3.7 (OXC) 8-10(MHD)**	**50% (40-60)**	**nk**	**Liver**	**No autoinduction**
PHT	**70-100**	**22 hrs**	**90% (88-93)**	**0.5-1.0 (0.8)**	**Liver**	**High oral doses-decreased absorption-saturation**
VPA	**90%**	**9-16 hrs**	**90% (5-15%!)**	**0.14-023 (0.2)**	**Liver 100% Beta-oxidation glucuronidation**	**Enzyme inhibition**

Pharmacokinetics

Drug	Bio-avalability	Half life*	Protein Binding *	Metabolism	Unique features
DZP	95-97%	Elimination 36 hrs Distribution 1 hr	95%	Liver	Redistributed in adipose tissue
Clorazepate	100%	Elimination 2.3 hrs Metabolite ~46 hrs	95%	Liver	Prodrug-active metabolite-desmethlyDZM
Midazolam		Elimination ~2 hrs Distribution 4-8 min	95%	Liver	Short acting
Clonazepam	90%	20-40 hrs	85%	Liver	Dose: 0.01 to 0.03 mg/kg/d
Lorazepam		Elimination 14hrs Distribution 2-3 h	90%	Liver Glucuronidation	Oral bioavailability less due to first pass effect
Clobazam	90%	10-30 hrs	85%	Liver	Less tachyphylaxis (tolerance)

Ref: Greenfield & Co. Wyllie's Treatment of Epilepsy; 6th edition, chapter 55

Valproate Protein Binding

- Highly bound to serum proteins- Binding appears to be saturable at therapeutic concentrations, with the free fraction of VPA increasing as the total concentration increases.
- 7% at 50 mg/L, to 30% at 150 mg/L.
  - With only 3 x increase in the total concentration of VPA, from 50 to 150 mg/L, the free level of VPA would increase more than 10 times, from 3.5 to 45 mg/L.
- Free level proportion is higher in higher serum levels.
- At high doses, check free levels as well.

Drug interactions

- Pharmacodynamic –more frequent
  - Sedation with other GABA+ drugs
- Diazepam –high protein bound
  - VPA may increase DZM levels
- Lorazepam- glucuronidation
  - VPA inhibits LZM metabolism
- Enzyme inducers- enhance elimination of all
- Clobazam-
  - Affected by many enzyme inducers including CBD

Drug	Effect	Enzymes Involved
Carbamazepine	Inducer	CYP(1A2, 2B6, 2C, 3A4), EH, UGT
Ethosuximide	None	
Felbamate	Inhibitor Inducer	CYP2C19, beta oxidation CYP3A4
Gabapentin	None	
Lamotrigine	Weak inducer	UGT
Levetiracetam	None	
Oxcarbazepine	Inhibitor Inducer	CYP2C19 CYP3A4, UGT
Phenobarbital/primidone	Inducer	CYP(1A2, 2B6, 2C, 3A4), EH, UGT
Phenytoin	Inducer	CYP(1A2, 2B6, 2C, 3A4), EH, UGT
Pregabalin	None	
Tiagabine	None	
Topiramate	Inhibitor Inducer	CYP2C19 CYP3A4
Valproate	Inhibitor	CYP2C9, EH, UGT
Zonisamide	None	

EH = epoxide hydrolase; UGT = UDP-glycosyltransferases.

Continuum Lifelong Learning Neurol 2007;13(4):91–105.

Newer AEDs, less Interactions

TABLE 4-2 **Effect of Adding a New Antiepileptic Drug on Serum Concentration of a Conventional Antiepileptic Drug**

	Conventional Antiepileptic Drug				
	Carbamazepine	Phenobarbital	Phenytoin	Primidone	Valproate
Gabapentin	None	None	None	None	None
Lamotrigine	None	None	None	None	None
Levetiracetam	None	None	None	None	None
Oxcarbazepine	None	Mild increase	Possible increase	None	None
Pregabalin	None	None	None	None	None
Tiagabine	None	None	None	None	None
Topiramate	None	None	Possible increase	None	None

French JA, Gidal BE. Antiepileptic drug interactions. Epilepsia 2000;41(suppl 8):30–36. Adapted with permission from Wiley-Blackwell Publishing Ltd.

Continuum Lifelong Learning Neurol 2007;13(4):91–105.

	Pre-existing AED	First generation AEDs									Second-generation AEDs														
		CBZ	CLB	CNP	ETS	PB	PHT	PRM	VPA	ESL	FBM	GBP	LEV	LTG	LCM	PER	PGB	OXC	RTG	RFN	STP	TGB	TPM	VGB	ZNS
AED added																									
CBZ			2	3			4						5		6				7						
CLB[viii]				9																					
CNP[ix]			11																						
ETS[xii]							13		14																
PB			15	16			17	18					19		20										
PHT			21					22					23		24				25						
PRM			26			27	28						29												
VPA		30					31												34						35
ESL																		36							
FBM		37	38																						
GBP																									
LEV																									
LTG				39					40																
LCM																									
PER[xlii]																									
PGB												43													
OXC		44								45															
RTG[xlvi]														47											
RFN																									
STP[xlviii]																									
TGB																									
TPM																									
VGB																									
ZNS																									

	Marked increase in serum concentration
	Slight to moderate increase in serum concentraion
	No change
	No change anticipated
	Mild to moderate decrease in serum concentration
	Marked decrease in serum concentration
	Not known
	Complex or variable interaction (see note)

Ref: Zaccara and Perucca

PMID 25515681

TABLE 4-5 Drugs That Have Been Found to Increase the Serum Concentration of Antiepileptic Drugs, Presumably by Inhibiting Their Metabolism

Affected Drug	Non-antiepileptic Drug Category	Interfering Drug
Carbamazepine	Antiepileptic drugs	Felbamate[a], valproic acid[a], valpromide[a]
	Antidepressants	Fluoxetine, fluvoxamine, nefazodone, trazodone, viloxazine
	Antimicrobials	Clarithromycin, erythromycin, fluconazole, isoniazid, ketoconazole, metronidazole, ritonavir, troleandomycin
	Miscellaneous	Cimetidine, danazol, dextropropoxyphene, diltiazem, risperidone, quetiapine[a], ticlopidine, verapamil
Ethosuximide	Antimicrobials	Isoniazid
Lamotrigine	Antiepileptic drugs	Valproic acid
	Antidepressants	Sertraline
Phenobarbital	Antiepileptic drugs	Felbamate, phenytoin, sulthiame, valproic acid
	Antimicrobials	Chloramphenicol
	Miscellaneous	Dextropropoxyphene
Phenytoin	Antiepileptic drugs	Felbamate, oxcarbazepine, valproic acid[b]
	Antidepressants	Fluoxetine, fluvoxamine, imipramine, sertraline, trazodone, viloxazine
	Antimicrobials	Chloramphenicol, fluconazole, isoniazid, miconazole, sulfaphenazole
	Antineoplastic drugs	Doxifluridine, fluorouracil, tamoxifen, tegafur, tegafur-uracil (Uftoral)
	Miscellaneous	Allopurinol, amiodarone, azapropazone, cimetidine, chlorpheniramine, dextropropoxyphene, diltiazem, disulfiram omeprazole, phenylbutazone, sulfinpyrazone tacrolimus, ticlopidine, tolbutamide
Valproic acid	Antiepileptic drugs	Felbamate
	Antidepressants	Sertraline
	Antimicrobials	Isoniazid
	Miscellaneous	Cimetidine

The list should not be regarded as exhaustive.

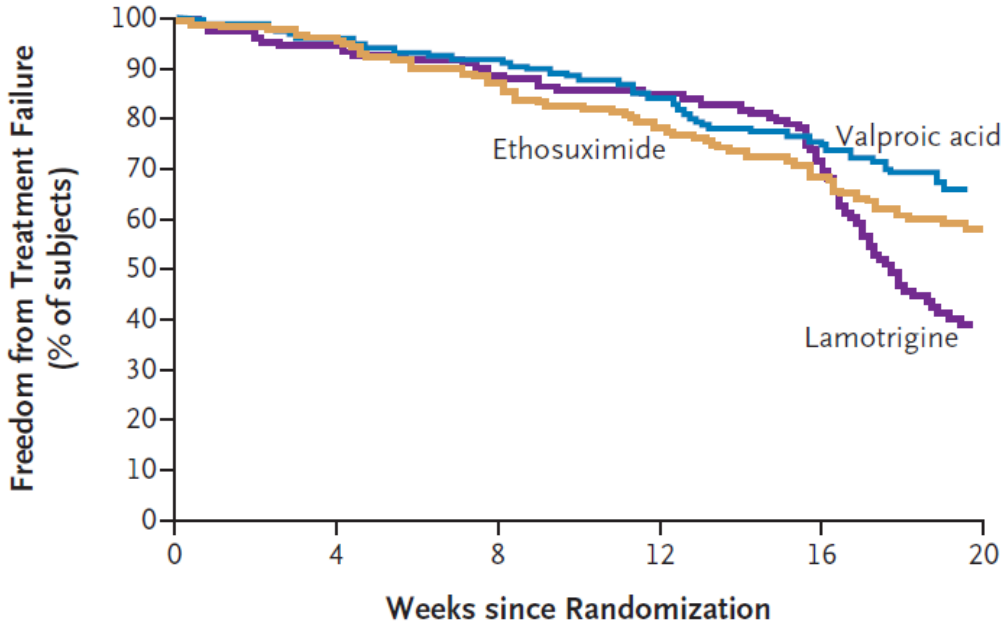
AEDs & Non-AEDs *Interaction*

Continuum Lifelong Learning Neurol 2007;13(4):91–105.

When starting enzyme Inducers …

- **Check other medications**
  - **Birth control pills**
  - **Oral anticoagulants**
  - **Immunosuppressants**
  - **Antiviral (HIV) drugs**

Absence Epilepsy Treatment



No. at Risk						
Ethosuximide	154	147	136	117	108	88
Lamotrigine	146	139	131	126	115	49
Valproic acid	146	139	132	124	111	86

Figure 1. Kaplan–Meier Curves for Freedom from Treatment Failure in the Three Study Groups.

VPA: 58%

ETX: 53%

LTG: 29%

Glauser T, et al. NEJM, 2010; 362; 790-99.

Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	1	1	3	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized onset tonic–clonic seizures	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Children with generalized-onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	1	0	7	Level A: ESM, VPA Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	0	0	1	Level A: None Level B: None Level C: None Level D: TPM, VPA

Epilepsia 2013: 54: 551-563