Pharmacokinetics of Psychotropic Drugs

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Teaching Points

Knowledge of pharmacokinetics is crucial for optimal pharmacotherapy, particularly in patients receiving combinations of medications.

Most clinically significant pharmacokinetic drug interactions involve induction or inhibition of metabolism.

Pharmacokinetic drug interactions are becoming increasingly predictable, due to advances in knowledge of the genetics of metabolic enzymes.

Pre Lecture Exam
Question 1

1. **Key pharmacokinetic parameters include: (choose one)**

A. Volume of distribution (V)
B. Half life ($t_{1/2}$)
C. Clearance (Cl)
D. Therapeutic index
E. All of the above
F. A, B, and C

Question 2

2. **After discontinuation, how long does it take to nearly completely (> 95%) clear a drug? (choose one)**

A. Clearance x half-life
B. 2 x half-life
C. 5 x half-life
D. Volume of distribution x clearance

Question 3

3. The two most important cytochrome P450 isoforms mediating drug interactions in psychiatric patients receiving combination therapies are: (choose two)

A. 1A2
B. 2C9/10
C. 2C19
D. 2D6
E. 2E1
F. 3A3/4

Question 4

4. Which of the following drugs is NOT an enzyme inducer? (choose one)

A. Carbamazepine
B. Valproate
C. Oxcarbazepine
D. Phenytoin
E. Phenobarbital
F. Primidone

Question 5

5. Which of the following drugs decrease plasma concentrations of hormonal contraceptives? (choose one)

A. Carbamazepine
B. Oxcarbazepine
C. Topiramate
D. Phenytoin
E. Phenobarbital
F. All of the above

Question 6

6. Which of the following drugs is NOT an enzyme inhibitor? (choose one)

A. Lithium
B. Bupropion
C. Fluoxetine
D. Valproate
E. Cimetidine
F. Erythromycin

Question 7

7. Which of the following drugs robustly increases plasma concentrations of lamotrigine? (choose one)

A. Carbamazepine
B. Valproate
C. Cimetidine
D. Gabapentin
E. Phenytoin

Question 8

8. Which of the following drugs have almost exclusively renal excretion? (choose one)

A. Gabapentin
B. Valproate
C. Lithium
D. Carbamazepine
E. A and C

Question 9

9. Monoamine oxidase inhibitor combination therapy is limited by:

A. Side effects (low to low-moderate therapeutic index)
B. Serious pharmacodynamic drug interactions
C. Allergic reactions (rashes)
D. Their exclusively renal excretion
E. A and B
F. None of the above

Question 10

10. Which of the following benzodiazepines has least potential for drug interactions?

A. Diazepam (a 2-keto-benzodiazepine)
B. Alprazolam (a triazolo-benzodiazepine)
C. Flurazepam (a 2-keto-benzodiazepine)
D. Lorazepam (a 3-hydroxy-benzodiazepine)

Outline

- **Concepts**
  Pharmacokinetics, Pharmacodynamics
- **Cytochrome P450**
  Isoforms, Substrates, Inhibitors, Inducers
- **Mood Stabilizers**
  Li, CBZ, VPA, lamotrigine
- **Antidepressants**
  SSRIs, SNRIs, bupropion, TCAs, MAOIs
- **Other Agents**
  Anxiolytics, Antipsychotics, Anticonvulsants, Ca blockers

Pharmacokinetics

- Time course of drug absorption, distribution, metabolism & excretion
- Drug transport to & from receptors
- What the body does to the drug

Pharmacodynamics

- Relationships between drug concentrations & responses
- Drug activity at receptors
- What the drug does to the body

Pharmacokinetic Concepts

Concept	Definition
V (vol of distrib)	Volume needed to contain drug at concentration same as plasma
$t_{1/2}$ (half life)	Time for [drug] to ↓ 50%
Cl (clearance)	Volume of blood cleared of drug per unit time

Pharmacokinetic Concepts

Concept	Relevance
V (vol of distrib)	Extracirculatory distribution (binding, lipophilicity)
	Loading dose (Load with V x [desired conc. change])
$t_{1/2}$ (half life) ($t_{1/2}$ = .7 x V / Cl)	Time to steady state = 5 x $t_{1/2}$
Cl (clearance)	Steady state concentration (C_{ss} = dose x dosing interval x F / Cl)

Pharmacokinetic Concepts

Concept	Example
V **(vol of dist)**	**Li - 1 L / kg; TCAs - 10 L / kg** **(dialysis effective); (dialysis ineffective)** **VPA - 0.2 L / kg** **(Load with 0.2 L/kg x 100 mg/L = 20 mg/kg)**
$t_{1/2}$ **(half life)**	**fluoxetine - 5 wk MAOI wait** **venlafaxine - 2 wk MAOI wait**
Cl **(clearance)**	**↑ [Li] in renal failure** **↑ [diazepam] in liver failure**

Absorption & First Pass Metabolism *

- **Bioavailability = % of oral dose reaching circulation as compared to IV**

  (F = % after absorption & first pass metab, < 2% for p.o. asenapine)

- **<u>Amount</u> affected by**
  - **Food**
    - **↑ ziprasidone, lurasidone, vilazodone absorption**
    - **↓ nefazodone absorption**
  - **Enteric / hepatic metabolism**
    - **Tyramine – MAO / Terfenadine - CYP3A4**
- **<u>Speed</u> affected by**
  - **Enteric motility (↑ with metoclopramide, ↓ with TCAs)**
  - **Formulation (solution > suspension > capsule > tab > enteric coated tab)**

Distribution

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- Lipophilicity & binding
- Many drugs 80 - 95% protein bound
  - Albumin – acids
  - α_1-acid glycoprotein – bases, neutral
  - Lipoproteins – bases, neutral
- Binding profiles
  - Alb: VPA, PHT, diazepam
  - Alb + α_1AG: CBZ, verapamil
  - Alb + α_1AG + LP: CPZ, TCAs
- ↓ binding in renal d. & hyperthyroidism

Excretion

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Rate = filtration + secretion – reabsorption

- **Filtration (glomerulus)**
  - **Affected by binding interactions**
  - **↓ in renal disease**
- **Secretion (proximal tubule)**
  - **Drugs compete for active transport**
- **Reabsorption (proximal > distal tubule)**
  - **Passive (high for lipophilic drugs)**
  - **Thiazides →↑ Li & Na reabsorption**
  - **Acidifying urine →↓ base reabsorption**

Metabolism *

Phase I ("Polarization") – Introduce/expose polar groups

- **Oxidation**
  - **Hydroxylation – alprazolam**
  - **Dealkylation – diazepam**
  - **Deamination – amphetamine**
  - **Sulfoxidation – chlorpromazine**
- **Reduction – clonazepam**
- **Hydrolysis – acetylsalicylate**

Phase II (Conjugation) – Form polar derivatives

- **Glucuronidation (UGTs) – oxazepam**
- **Sulfation (SULTs) – acetaminophen**
- **Methylation – norepinephrine**
- **Acetylation (NATs) – clonazepam, phenelzine**

Metabolites Compared to Parent Drugs

- **Longer $t_{1/2}$**
- **More water soluble**
- **Generally less active, but can be more active (hydroxylated, demethylated)**
- **Pharmacodynamics may be**
  - **Similar (CBZ-E vs. CBZ)**
  - **Different (m-CPP anxiogenic vs. trazodone anxiolytic)**

Active Metabolites

Carbamazepine	carbamazepine-10,11-epoxide
Oxcarbazepine	mono-hydroxy-derivitive (MHD)
Valproate	2-ene-valproate, 4-ene-valproate (toxic)
Amitriptyline	nortriptyline
Nortriptyline	hydroxy-nortiptyline
Imipramine	desipramine, hydroxy-imipramine
Desipramine	hydroxy-desipramine
Amoxapine	hydroxy-amoxapine
Fluoxetine	norfluoxetine
Sertraline	N-desmethyl-setraline (±)
Citalopram	di/desmethyl-citalopram
Venlafaxine	O-desmethyl-venlafaxine
Bupropion	hydroxy-bupropion
Trazodone	m-chlorophenylpiperazine (m-CPP)
Nefazodone	m-CPP, hydroxy-nefazodone

Active Metabolites

Diazepam	N-desmethyl-diazepam
Clorazepate	N-desmethyl-diazepam
Chlordiazepoxide	N-desmethyl-diazepam
Alprazolam	apha-hydroxy-alprazolam
Flurazepam	desalkyl-flurazepam
Buspirone	pyrimidinylpiperazine (1-PP)
Chlorpromazine	hydroxy-chlorpromazine
Thioridazine	mesoridazine
Haloperidol	reduced haloperidol
Loxapine	amoxapine
Clozapine	desmethyl-clozapine (±)
Risperidone	9-hydroxyrisperidone
Quetiapine	N-desalkyl-quetiapine
Aripiprazole	dehydo-aripirazole
Ziprasidone	S-methyl-dihydro-ziprasidone (±)

Pharmacodynamic Concepts

Concept	Definition / Relevance
Therapeutic index	Efficacy relative to toxicity
Dose-response curve	Linear, sigmoidal, curvilinear
Tolerance	↓ therapeutic or adverse effects with time
Withdrawal	Discontinuation effects
Response latency	Delay to onset of effects

Pharmacodynamic Concepts

Concept	Example
Therapeutic index	High for SSRIs, low for Li
Dose-response curve	Curvilinear for nortriptyline (therapeutic window)
Tolerance	BZ (sedation, anticonvulsant) opiates (analgesia)
Withdrawal	BZ (insomnia, anxiety)
Response latency	BZ – minutes Li, CBZ, VPA - days to wks

Drug Interactions

Pharmacokinetic

- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamic

- Direct - at same receptor site
  - AMI + CPZ anticholinergic toxicity
- Indirect - at different receptor sites
  - MAOI + SSRI serotonin toxicity?

Interaction Potential

- Low therapeutic index
- Long half-life
- Nonlinear kinetics
- Active metabolites
- Potent metabolic inhibition / induction
- Single metabolic route
- CYP2D6, CYP3A4,5,7

P450 Notation

CYP2D6

CYP - CYtochrome P (protein) 450
(wave length CO absorption)
2 - family (> 40% homology)
D - subfamily (> 55% homology)
6 - gene

Key Isoforms for Drug Metabolism

Isoform	Substrates	Inhibitors	Inducers
CYP1A2	TCAs,cloz,olanz	cipro, fluvoxamine	cig smoke,omep
CYP2C9/10	phenytoin,THC S-warfarin	fluvoxamine	rifam,barb
CYP2C19	BZs,TCAs	fluox,fluvox	rifampin
CYP2D6	TCAs,parox,mirtaz venla, ±fluox	parox,fluox ±fluvox, ±sertra disulfiram	-
CYP2E1	Etoh		Etoh,INH
CYP3A4,5,7	BZs,CBZ Sertraline Nefazodone TCAs, mirtaz Ca blockers Oral contraceptives	fluoxetine fluvoxamine nefazodone diltiazem verapamil macrolides	CBZ phenytoin phenobarb rifampin St John's wort

CYP2D6

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Substrates	Inhibitors	Inducers
atomoxetine	bupropion	
duloxetine	fluoxetine	
± fluoxetine	± fluvoxamine	
± mirtazapine	paroxetine	
paroxetine	± sertraline	
venlafaxine	moclobemide	
2° & 3° tricyclics (hydroxylation)		
trazodone	fluphenazine	-
	haloperidol	
± clozapine	perphenazine	
haloperidol	thioridazine	
fluphenazine		
perphenazine		
risperidone		
thioridazine	amiodarone	
	cimetidine	
codeine	methadone	
mexiletine	quinidine	
IC antiarrhythmics	ritonavir et al	
β blockers		

CYP3A4,5,7

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Substrates	Inhibitors	Inducers
± citalopram		CBZ
± mirtazapine	fluvoxamine	phenobarbital
nefazodone		phenytoin
reboxetine	nefazodone	
sertraline		
3° tricyclics	diltiazem	
(demethylation)	verapamil	
vilazodone		
lurasidone		
quetiapine		
alprazolam		
diazepam		
midazolam		
triazolam		
buspirone	cimetidine	dexamethasone
CBZ	imidazoles	rifampin
	macrolides	
Ca blockers	naringenin	
H1 blockers		
local anesthetics		
macrolides		
quinidine		
steroids		

Inhibition Profiles

Potency	CYP2D6	CYP3A4,5,7
highest	quinidine paroxetine fluoxetine bupropion	ketoconazole clarithromycin nefazodone
intermediate	sertraline	fluvoxamine
lowest	fluvoxamine nefazodone venlafaxine erythromycin ketoconazole	sertraline desmethylsertraline

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Inhibitors

TCAs, MAOIs
bupropion
fluoxetine
fluvoxamine
paroxetine
± sertraline
nefazodone

antipsychotics
acute ethanol
disulfiram
methylphenidate
diltiazem
verapamil
valproate

azole antifungals
chloramphenicol
ciprofloxacin
cotrimoxazole
macrolides
metronidazole

allopurinol
cimetidine
omeprazole
phenylbutazone
propranolol
propoxyphene
quinidine

Inducers

barbiturates
carbamazepine
phenytoin
primidone

cigarette smoke
chronic ethanol

isoniazid
rifampin

glutethimide
omeprazole

Genetic Polymorphisms

CYP2D6 (Poor Metabolizers)

Autosomal recessive; 5-10% whites, 1% Asians

Substrates: 2° & 3° TCAs, duloxetine, paroxetine, venlafaxine, ± fluoxetine, thioridazine

IC antiarrhythmics, β-blockers

CYP2C19 (Poor Metabolizers)

Recessive; 3-5% whites, 15-20% Asians

Substrates: 3° TCAs, diazepam, barbiturates omeprazole, S-mephenytoin

N-acetyltransferase (Slow Acetylators)

Autosomal recessive; 50% whites, 10% Asians

Substrates: isoniazid, clonazepam, phenelzine

Special Populations

Group	Protein binding	Hepatic elimination	Renal elimination
Children	(=)	(↑)	(↑)
Elderly	(=)	(= ↓)	↓
Pregnant	(=↓)	(= ↓ ↑)	↑
Manic	(=)	(=)	(↑)
Renal d.	↓	↓	↓
Liver d.	(= ↓)	↓	(= ↓)

Formulations of Selected Medications

Medication	Oral tab/cap/sl	Oral fluid	Rapid Acting injectable	Long Acting injectable
Asenapine	SL			
Aripiprazole	+, ODT	+	IM	
Carbamazepine	+, ER	+		
Chlorpromazine	+	+	IM, IV	
Divalproex	+, ER	+	IV	
Lamotrigine	+, ER, ODT			
Lithium	+, ER	+		
Olanzapine	+, ODT		IM	IM
Olanzapine+fluoxetine	+			
Quetiapine	+, ER			
Risperidone	+, ODT	+		IM
Ziprasidone	+		IM	

ER = Extended Release; ODT = Orally Disintegrating Tab; IM = Intramuscular; IV = Intravenous; SL = Sublingual.

Mood Stabilizer and Anticonvulsant Metabolism

Drug	Substrate of	Induces / Inhibits
lithium	renal excretion	-
carbamazepine	3A4, 3A5-7	induces 3A4,5,7 ...
valproate	conjugation β-hydroxylation P450 oxidation	weak inhibitor
phenytoin	2C9/10, ± 2C19	induces 3A4,5,7, ...
barbiturates	2C19	induce 3A4,5,7, ...
lamotrigine	UGT1A4?	mildly self
gabapentin	renal excretion	-

Lithium

- 100% absorbed; F = 100%
- 0% bound; V = 1 L / kg
- $t_{1/2}$ = 24 h; Cl = 10 - 40 mL / min
- Cl = .25 x creatinine Cl
- 900 - 2400 mg / d; .6 - 1.2 mEq / L
- No metabolites
- No metabolic interactions
- 100% renal excretion
- Renal excretion interactions
- Low therapeutic index -> neurotoxicity

Drugs & Factors Affecting Lithium Clearance & Levels *

↓ Clearance (↑ Levels)	= Clearance (= Levels)	↑ Clearance (↓ Levels)
Thiazides	Amiloride Furosemide	Acetazolamide Mannitol
Older NSAIDs COX-2 Inhibitors	ASA (?) Acetaminophen Sulindac (NSAID)	Aminophylline Caffeine (?) Theophylline
ACE inhibitors AT_1 antagonists		Pregnancy Mania (?)
Dehydration Sodium depletion Renal impairment Advanced age		

? = Conflicting data,

NSAIDs = Non-steroidal Anti-Inflammatory Drugs (e.g. ibuprofen), COX-2 = cyclooxygenase-2 (e.g. celecoxib)

ACE = Angiotensin I Converting Enzyme (e.g. lisinopril), AT_1 = Angiotensin II receptor Type-1 (e.g. losartan)

Carbamazepine

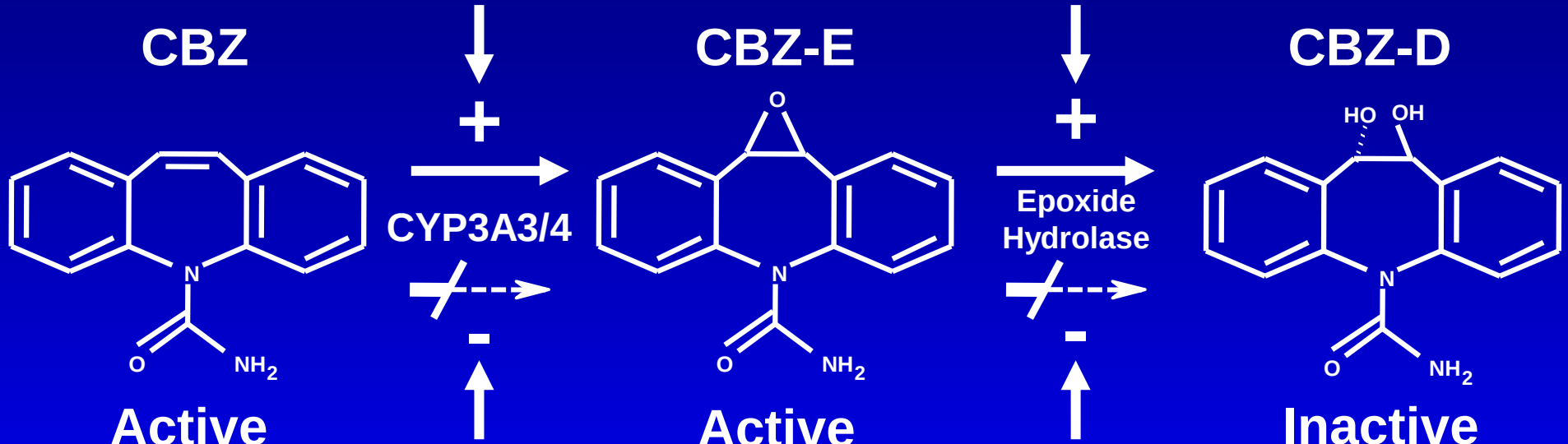
- Erratic absorption; F = 80%
- 75% bound; V = 1 L / kg
- t1/2 = 24 h; Cl = 25 mL / min (pre-induction)

  t1/2 = 8 h; Cl = 75 mL / min (post-induction)
- 400 - 1600 mg / d; 4 - 12 mcg / mL
- Active CBZ-10,11-epoxide metabolite (t1/2 6h)
- Complex kinetics & multiple interactions
- > 40% 10,11-epoxidation [mostly 3A4,3A5-7]
- Autoinduction, heteroinduction
- Low therapeutic index (neurotoxicity)

Carbamazepine Metabolism

↓ CBZ Levels with
CARBAMAZEPINE* (++)
FELBAMATE (+)
PHENOBARBITAL* (++)
PHENYTOIN* (++)
PRIMIDONE (++)

↓ CBZ-E Levels with
carbamazepine (+)
phenobarbital (+)
phenytoin (+)
primidone (+)



Active
Parent Drug

↑ CBZ Levels with
ACETAZOLAMIDE
cimetidine*
CLARITHROMYCIN*
DANAZOL*
DILTIAZEM*
ERYTHROMYCIN*
FLUOXETINE*
FLUVOXAMINE*
gemfibrozil
ISONIAZID
NEFAZODONE*
nicotinamide
PROPOXYPHENE
VERAPAMIL*

Active
Epoxide Metabolite

↑ CBZ-E Levels with
lamotrigine (-?)
progabide (-)
VALPROATE (-)
VALPROMIDE (--)

Inactive
Diol Metabolite

* molecular bichemical evidence supports CYP3A3/4

Ketter TA, et al: J Clin Psychopharmacol 1991;11:198-203,306-13.

Carbamazepine Decreases Levels of Other Drugs

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(A Partial List)

Antidepressants
Bupropion
Citalopram
Mirtazapine (?)
Tricyclics

Antipsychotics
Aripiprazole
Clozapine
Fluphenazine (?)
Haloperidol
Olanzapine
Quetiapine (?)
Risperidone
Thiothixene (?)

Ziprasidone

Anxiolytics/Sedatives
Alprazolam (?)
Buspirone
Clonazepam
Midazolam
Zopiclone?

Stimulants
Methylphenidate
Modafinil

Analgesics
Alfentanil
Buprenorphine
Fentanyl (?)

Levobupivacaine
Methadone
Tramadol

Anticonvulsants
Carbamazepine
Ethosuximide
Felbamate
Lamotrigine
Oxcarbazepine
Phenytoin
Primidone
Tiagabine
Topiramate
Valproate
Zonisamide

Anticoagulants
Dicumarol (?)

Phenprocoumon
Warfarin

Antimicrobials
Caspofungin
Doxycycline

Antivirals
Delavirdine
Protease inhibitors

Immunosuppressants
Cyclosporine (?)
Sirolimus
Tacrolimus

Muscle Relaxants
Doxacurium

Pancuronium
Rapacuronium
Rocuronium
Vecuronium

Steroids
Hormonal contraceptives
Dexamethasone
Mifepristone
Prednisolone

Others
Bepridil
Dihydropyridine CCBs
Oxiracetam (?)
Paclitaxel
Quinidine
Remacemide (?)
Repaglinide
Theophylline (?)
Thoraloralyroid hormones

Ketter TA, et al. In: Schatzberg AF, Nemeroff CB (eds.). The American Psychiatric Press Textbook of Psychopharmacology (3rd ed.). American Psychiatric Press, Washington, DC 2003:581-606.

Selected Drugs that Increase Levels of Carbamazepine *

(A Partial List)

Antidepressants
Fluoxetine
Fluvoxamine
Nefazodone

Antimicrobials
Isoniazid
Quinupristin/dalfopristin

Macrolide Antibiotics
Clarithromycin
Erythromycin
Flurithromycin
Josamycin
Ponsinomycin

Calcium Channel Blockers
Diltiazem
Verapamil

Hypolipidemics
Gemfibrozil
Nicotinamide

Others
Acetazolamide
Cimetidine
Danazol
Omeprazole
d-Propoxyphene
Ritonovir (?)
Ticlopidine (?)
VPA (increases CBZ-E)

Ketter TA, et al. In: Schatzberg AF, Nemeroff CB (eds.). The American Psychiatric Press Textbook of Psychopharmacology (3rd ed.). American Psychiatric Press, Washington, DC 2003:581-606.

CYP3A4-Mediated Carbamazepine Drug Interactions

CBZ →↓ Drug	Drug →↑ CBZ	Drug →↓ CBZ
3° tricyclics (demethylation)	Fluoxetine	CBZ
Ca blockers	fluvoxamine	phenobarbital
CBZ	Nefazodone	phenytoin (?)
benzodiazepines	Ca blockers	
dexamethasone	danazol	
oral contraceptives	cimetidine	
prednisolone	clarithromycin	
local anesthetics	erythromycin	
ethosuximide		

Valproate

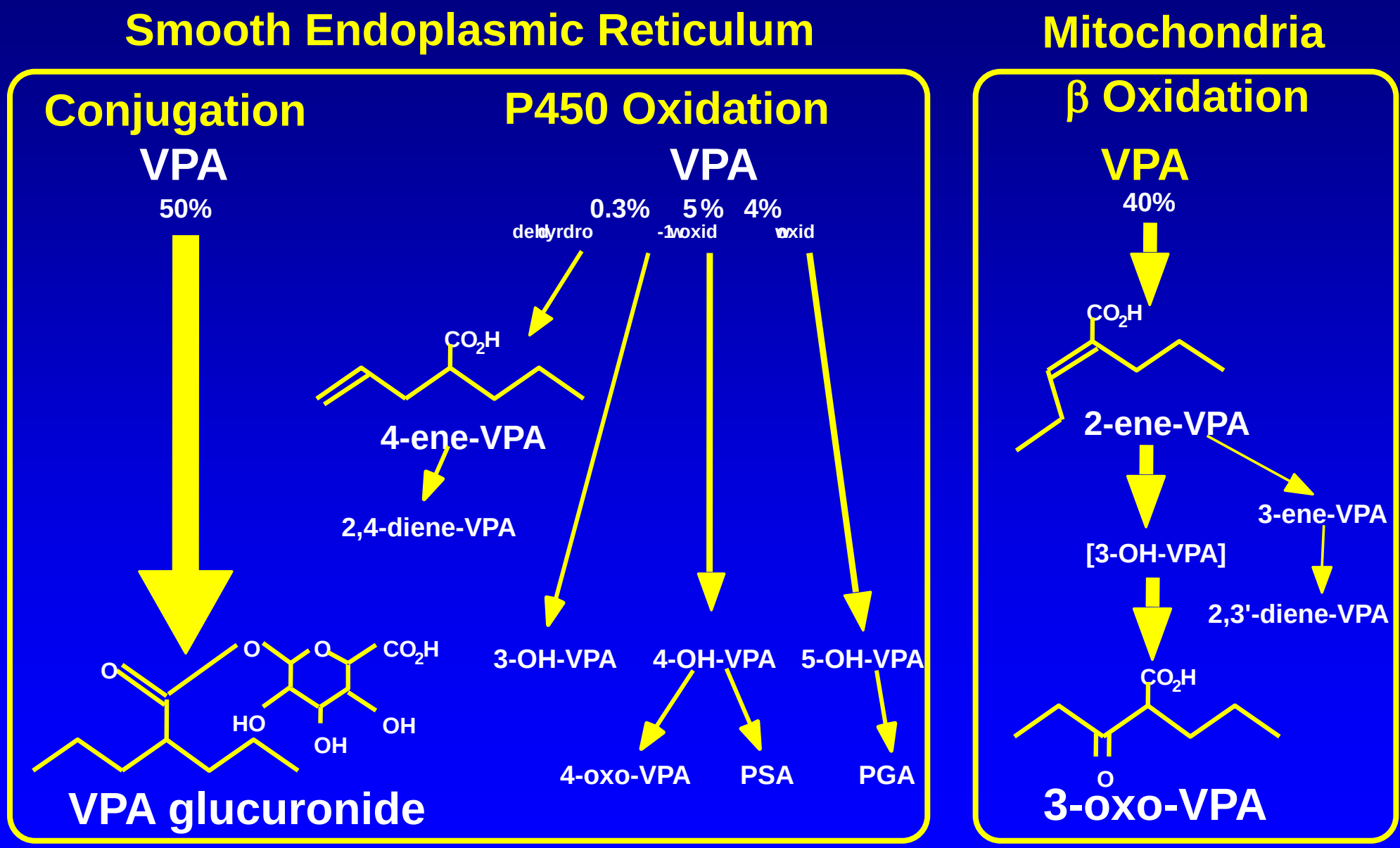
- 100% absorbed; F = 100%
- 80 - 90% bound (saturable); V = 0.1 - 0.2 L / kg
- t1/2 = 12 h; Cl = 10 mL/ min
- 750 - 4000 mg / d; 50 - 125 mcg / mL
- Binding saturation-lower % bound at hi levels
- "Sublinear" kinetics, binding interactions
- 3 elimination routes metabolites

  50% conjugation glucuronides

  40% β oxidation 2-ene-valproate, ...

  10% P450 oxidation 4-ene-valproate, …
- Some metabolic interactions
- Low-mod therapeutic index (g.i., neurotoxicity)

Valproate Metabolism



Potter WZ, Ketter TA: Can J Psychiatry 1993;38:S51-S56.

Valproate-Plasma Protein Binding Interactions

VPA →↑ Free Drug

CBZ

diazepam

phenytoin

tiagabine

tolbutamide

warfarin

Drug →↑ Free VPA

ASA

NSAIDs

Valproate Metabolic Interactions

VPA →↑ Drug	Drug →↑ VPA	Drug →↓ VPA
amitriptyline	ASA	CBZ
CBZ-E	cimetidine	± lamotrigine
diazepam	fluoxetine	mefloquine
ethosuximide	felbamate	phenobarbital
lamotrigine	erythromycin	phenytoin
lorazepam	phenothiazines	rifampin
nortriptyline		
phenobarbital		
phenytoin		
zidovudine		

Lamotrigine

- F = 98%; 55% bound; V = 1 L / kg
- Rx $t_{1/2}$ (h) Cl (mL/min) dose (mg/d)

monoRx	28	40	200 [100 - 400]
with CBZ	14	80	400 [200 - 800]
with VPA	56	20	100 [50 - 200]

- Linear kinetics
- Inactive glucuronide metabolites
- LTG $\rightarrow$↑CBZ neurotoxicity (dynamic vs ↑ CBZ-E)
- LTG $\rightarrow \pm \downarrow$ VPA
- VPA, ± sertaline $\rightarrow \uparrow$ LTG
- CBZ, PHT, PB, PRIM , BCPs $\rightarrow \downarrow$ LTG

Lamotrigine Titration Influenced by Valproate and Carbamazepine *

Lamotrigine Titration in Adults[1,2]

Week	Dose (mg/day)
1	25
2	25
3	50
4	50
5	100
6	200
Maintenance	200-400 as clinically indicated

- Double lamotrigine dose with carbamazepine
- Halve lamotrigine dose with valproate

[1] Guberman et al. Epilepsia. 1999; [2] Physicians' Desk Reference. 200.

Lamotigine Metabolic Interactions

Drug →↑ LTG	Drug →↓ LTG
valproate	CBZ
	oral contraceptives
	phenobarbital
	Phenytoin
	primidone
	rifampin

Key Isoforms For Antidepressant Metabolism

Isoform	Substrates	Inhibitors	Inducers
CYP1A2	TCAs, ± mirtaz,dulox	fluvoxamine	cigs, omep
CYP2C19	± citalopram, TCAs	fluox, fluvox	rifampin
CYP2D6	± fluoxetine ± mirtazapine paroxetine dulox/venlafaxine TCAs, trazodone	bupropion fluoxetine ± fluvoxamine paroxetine ± sertraline	-
CYP3A4,5,7	± citalopram ± mirtazapine nefazodone reboxetine sertraline, TCAs	fluvoxamine nefazodone ± sertraline	CBZ phenytoin phenobarb rifampin

Tricyclic Antidepressants

- 100% absorbed; F = 20 - 70%
- 90% bound; V = 10 - 30 L / kg
- $t_{1/2}$ = 24 h; Cl = 300 - 1700 mL/ min
- 150 - 300 mg/d; 150 - 300 ng/mL (AMI,IMI,DMI)
  75 - 150 mg / d; 75 - 150 ng/mL (NORT)
- Active demethylated & hydroxylated metabs: amitriptyline (NORT), imipramine (DMI)
- DMI (2-OH-DMI), NORT (10-OH-NORT) CMI (desmethyl-CMI), DOX (desmethyl-DOX)
- 2° / 3° amines - 2-, 8-, 10-hydroxylation [2D6] (rate limiting)
- 3° amines - N-demethylation [1A2,2C19,3A4,5,7]
- Low therapeutic index (anticholinergic)

Tricyclic Interactions

Drug →↑ TCA

Via 2D6

fluoxetine
± sertraline
paroxetine
haloperidol
phenothiazines
methadone
propafenone
quinidine

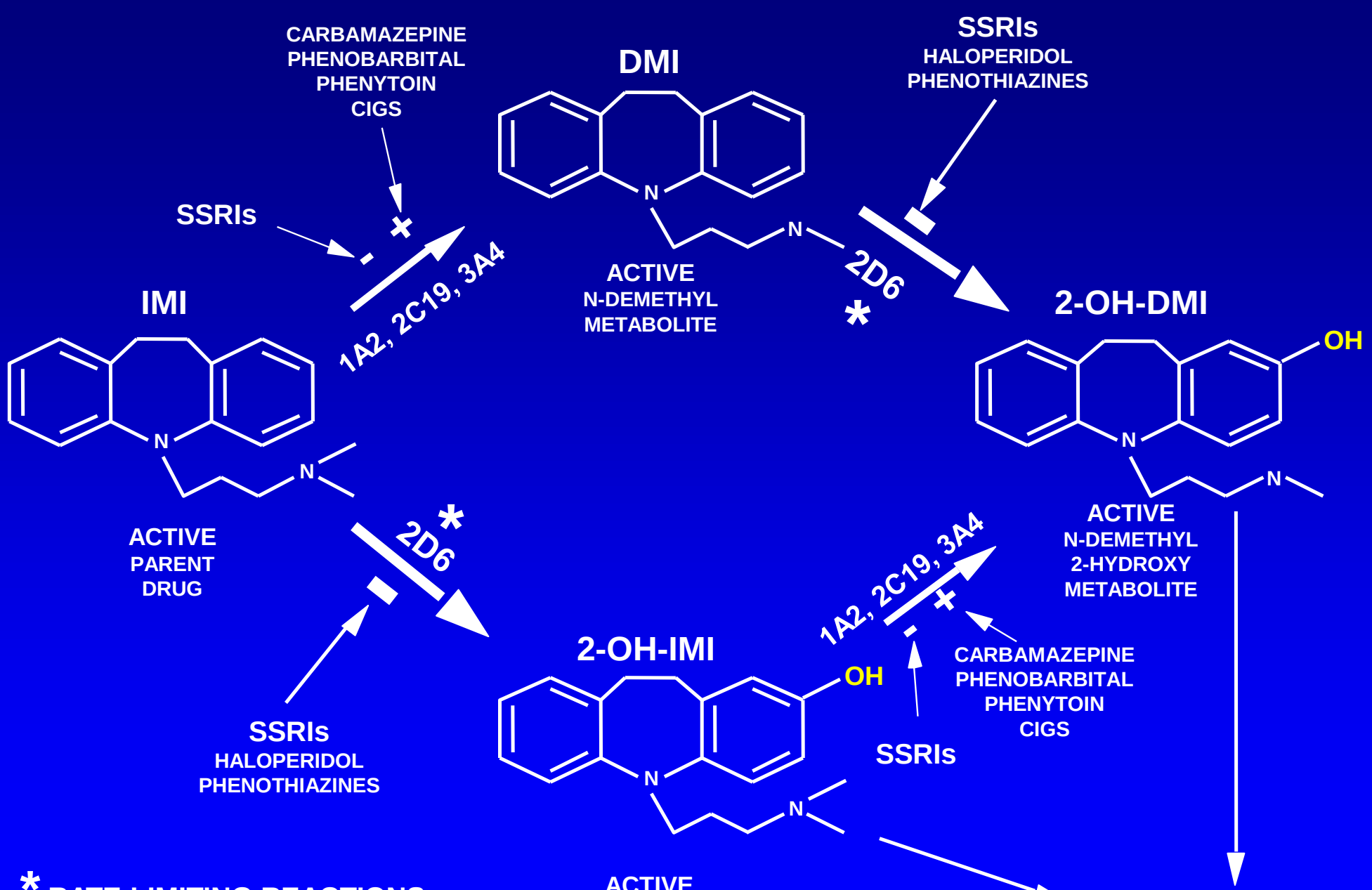
Via ?

methylphenidate(?)
disulfiram
acute ethanol
valproate (?)
azole antifungals (?)
BCPs (?)
cimetidine
chloramphenicol

Tricyclic Interactions

Drug →↓ TCA	TCA →↑ Drug
carbamazepine	phenytoin (?)
chronic ethanol	warfarin (?)
cigarette smoke	
phenobarbital	
phenytoin	
rifampin (?)	

Imipramine Metabolism



* RATE LIMITING REACTIONS

SSRIs & SNRIs

- SSRIs - fluoxetine, sertraline, paroxetine, fluvoxamine
- SNRI - duloxetine, venlafaxine
- ↓ side effects, ↑ therapeutic index vs TCAs

Drug	Paroxetine	Fluoxetine	Sertraline	Fluvoxamine	Venlafaxine	(es)Citalopram
Inhibits	(2D6)	(2D6,3A4)	(±2D6)	(1A2,2C9,3A4)	-	±(1A2,2C19,2D6)
Substrate	(2D6)	(2D6,3A4)	(3A4)	?	(2D6)	(3A4,2C19)
Metabolite	-	+	±	-	+	±

Duloxetine- CYP1A2 and CYP2D6 substrate , and modest CYP2D6 inhibitor

Fluoxetine

- Well absorbed; F > 60%
- 95% bound; V = 20 - 45 L / kg
- $t_{1/2}$ = 4 d; Cl = 300 mL/ min
- 20 - 80 mg / d
- Norfluoxetine metabolite (active, $t_{1/2}$ = 7-14 d)
- 5 week wait for MAOIs
- CYP2D6 substrate (40%)
- CYP2D6 > CYP3A4 inhibitor
- Nonlinear kinetics (saturation)
- High therapeutic index

Fluoxetine Interactions

*

Fluoxetine →↑ Drug

Via 2D6

AMI, IMI
NORT, DMI
fluphenazine
haloperidol
clozapine
dextromethorphan
oxycodone
atomoxetine
duloxetine
venlafaxine

Via 3A4, 3A5-7

alprazolam
diazepam
+/-carbamazepine

Via 2C19

moclobemide
diazepam
± phenytoin

Via ?

valproate

Paroxetine

- 100% absorbed
- Large first pass, F dose dependent
- 95% bound; V = 17 L / kg
- $t_{1/2}$ = 21 h; 10 - 50 mg / d
- Inactive metabolites
- 2 week wait for MAOIs
- CYP2D6 inhibitor & substrate
- Nonlinear kinetics (saturation)
- Increases TCA levels
- High therapeutic index

Paroxetine Interactions

Paroxetine →↑ Drug

Via 2D6

AMI, IMI

NORT, DMI

phenothiazines

IC antiarrhythmics
(propafenone, flecainide, encainide)

beta blockers

atomoxetine

Fluvoxamine

- 94% absorbed; F = 53%
- 80% bound; V = 20 L / kg
- $t_{1/2}$ = 16 h; Cl = 1600 mL/ min
- 50 - 300 mg / d
- Inactive metabolites
- Novel interaction profile
- High therapeutic index

Fluvoxamine Interactions

Fluvoxamine →↑ Drug

Via 1A2	Via 3A4,5,7	Via 2C9/10
AMI, IMI, CMI	alprazolam	phenytoin
maprotiline	diazepam	warfarin
clozapine	carbamazepine	
olanzapine		Via 2D6
methadone		
caffeine		haloperidol
phenacetin		
propranolol		
theophylline		

Sertraline

- Absorption minimally ↑ with food
- 98% bound; V = 20 L / kg
- $t_{1/2}$ = 26 h; 50 - 200 mg / d
- Desmethylsertraline metabolite (± active, $t_{1/2}$ = 3 d)
- 2 week wait for MAOIs
- CYP3A4,5,7 substrate
- CYP2D6 > CYP3A4,5,7 inhibitor
- At 50 mg / day less effect on TCA levels than fluoxetine, paroxetine, (but more significant at 200 mg/day)
- High therapeutic index

Citalopram (Racemic *S*- and *L*-citalopram)

- Absorption rapid, not affected by food; F = 80%
- 80% bound; V = 12 L / kg
- $t_{1/2}$ = 35 h; Cl = 330 mL/ min
- 10 - 40 mg / d
- Demethylcitalopram metabolite (± active, via 2C19, 3A4, ± 2D6)
- Didemethylcitalopram metabolite (± active, via 2D6)
- 2 week wait for MAOIs
- Weak 1A2, 2C19, 2D6 inhibitor
- High therapeutic index (but recent cardiac concerns)
- Contraindicated in canine acral lick syndrome

Citalopram Interactions

Citalopram →↑ Drug

Via 2D6

DMI
(citalopram given with IMI)
metoprolol

Drug →↑ Citalopram

Via ??

cimetidine
CMI
fluvoxamine

Escitalopram (*S*-enantiomer of citalopram)

- Absorption rapid, not affected by food; F = 80%
- V = 20 L / kg
- $t_{1/2}$ = 27 h; Cl = 600 mL/ min; linear kinetics
- 10 - 20 mg / day
- S-Demethylcitalopram metabolite (± active, via 2C19, 3A4, ± 2D6)
- S-Didemethylcitalopram metabolite (± active, via 2D6)
- Decreased clearance with hepatic impairment
- Contraindicated in canine acral lick syndrome
- 2 week wait for MAOIs
- Weak 2D6 inhibitor
- High therapeutic index

Venlafaxine

- 92% absorbed; F = 10%
- 27% bound; V = 8 L / kg
- $t_{1/2}$ = 5 h; Cl = 1400 mL/ min
- 75 - 375 mg / day
- Desmethylvenlafaxine metabolite (active, $t_{1/2}$ = 11 h)
- 2 week wait for MAOIs
- CYP2D6 substrate
- Modest inhibition of CYP2D6
- High therapeutic index

Desmethyl-venlafaxine

- F = 80%
- 30% bound; V = 3.4 L / kg
- $t_{1/2}$ = 11 h
- 50 mg / d (higher doses no more effective)
- 2 week wait for MAOIs
- UGT glucuronidation > CYP3A4 N-demethylation
- Minimal inhibition of CYP2D6
- High therapeutic index

Duloxetine

- $t_{1/2}$= 12 hrs, similar in men & women
- V_d = 23 L / kg
- 90% bound to albumin and alpha1-acid protein
- Metabolized by CYP1A2 and CYP2D6
  - smoking reduces AUC by 1/3
  - fluvoxamine (CYP1A2 inhibitor) increases AUC 6-fold
- C_{max} = 6 h (a.m. administration)
  - p.m. administration delays C_{max} 3 h, increases AUC 10%
  - food delays C_{max} 6-10 h

Vilazodone

- 72% absorbed (with food)
- Food increases absorption by 75%
- 96-99% bound
- $t_{1/2}$ = 25 h
- 10 mg qd x 1 wk → 20 mg qd x 1 wk → 40 mg qd
- CYP3A4 > CYP2C19, CYP2D6 substrate
- ketoconazole → ↑ vilazodone
- Unknown if 3A4 inducers → ↓ vilazodone
- Do NOT give with MAOIs

Vortioxetine

- 75% absorbed; V = 37 L / kg
- 98% bound
- $t_{1/2}$ = 66 h
- 10 mg qd x 1 wk → 20 mg qd
- CYP2D6 > other CYPs substrate
- bupropion, FLX, PXT, quinidine → ↑ vortioxetine
- rifampin, CBZ, PHT may → ↓ vortioxetine
- Do NOT give with MAOIs

Levomilnacipran

- 92% absorbed; V = 7 L / kg
- 22% bound
- $t_{1/2}$ = 12 h
- 20 mg qd x 2 d → 40 mg qd x 2 d → 80 mg qd x 2d → 120 mg qd
- CYP3A4 > other CYPs substrate
- ketoconazole → ↑ levomilnacipran
- Do NOT give with MAOIs

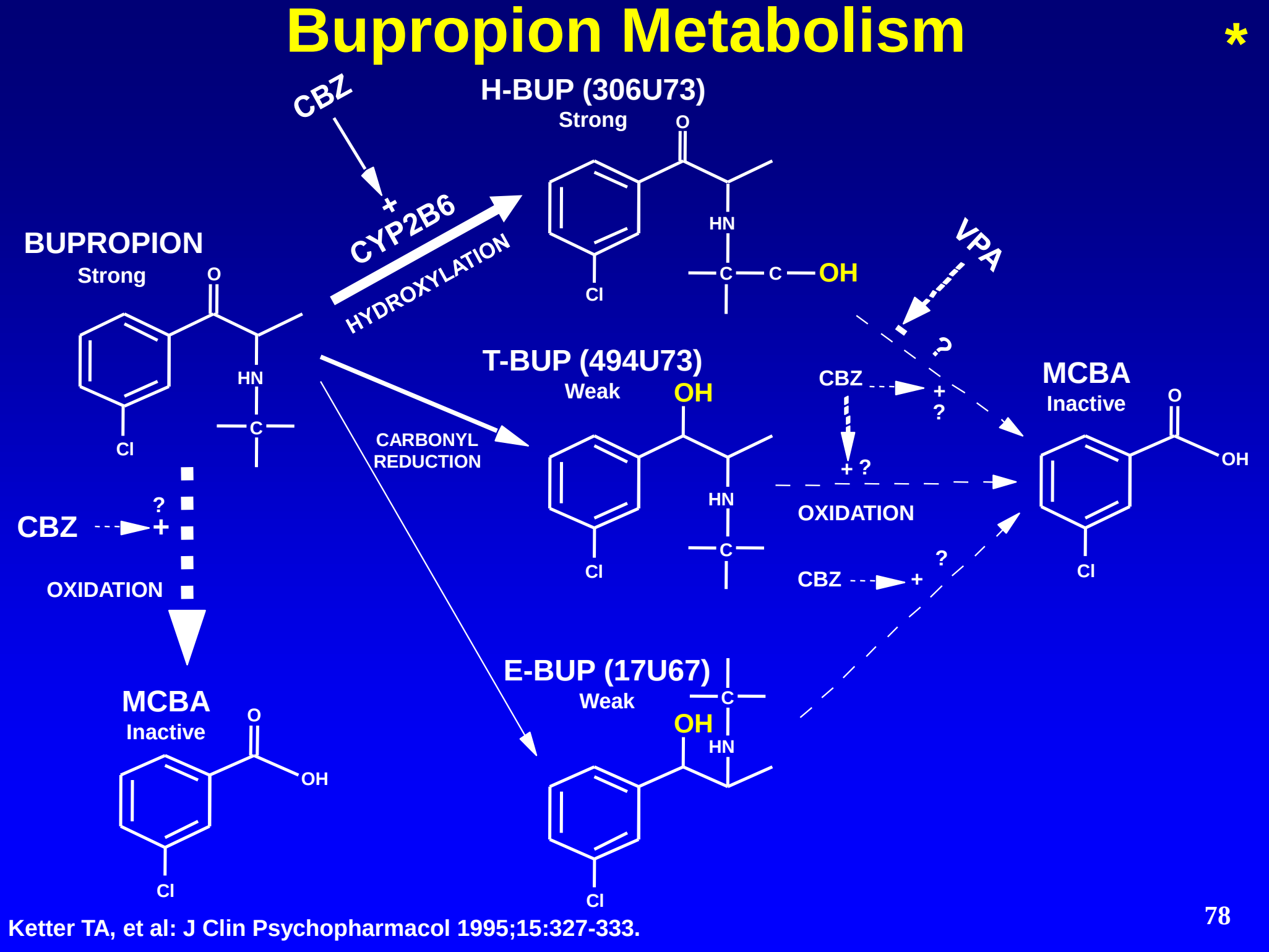
Pharmacokinetics of Selected SSRIs and SNRIs

	Fluoxetine	Sertraline	Paroxetine	Fluvoxamine	Venlafaxine	Citalopram
drug $t_{1/2}$	4 d	26 h	21 h	16 h	5 h	35 h
metab $t_{1/2}$	7 d	3 d	-	-	11h	-
Binding	95%	98%	95%	80%	27%	80%
Nonlinear	+		+			
2D6 inhib	++	±	++	±	±/-	±
3A4 inhib	+	±		+		
1A2 inhib				++		±
2C9 inhib	+	±		+		
2C19 inhib	+	+		+		±

Bupropion

- 90% absorbed
- 85% bound; V = 20 L / kg
- t1/2 = 20 h; Cl = 2300 mL / min
- 150 - 400 mg / day; > 10 ng / mL (?)
- Extensive, CBZ-inducible metabolism
- Hydroxy-BUP (morpholinol) via CYP2B6
  - Threohydro-BUP via carbonyl reductase
  - Erythrohydro-BUP via carbonyl reductase
- 3 main active metabolites: $t_{1/2}$ AUCss cf BUP
  - hydroxy-BUP (morpholinol) 20 h 17 x BUP
  - threohydro-BUP 37 h 7 x BUP
  - erythrohydro-BUP 33 h 1.5 x BUP
- High H-BUP levels in poor response (?)
- CYP2D6 potent inhibitor

Bupropion Metabolism



Ketter TA, et al: J Clin Psychopharmacol 1995;15:327-333.

Bupropion Interactions

Drug →↓ BUP
Via ?
carbamazepine
phenobarbital ?
phenytoin ?

Drug →↑ BUP
Via 2B6
orphenadrine
ifosfamide ?
cimetidine ?

BUP →↓ Drug
no evidence thus far

BUP →↑ Drug
Via 2D6
Desipramine
venlafaxine

Trazodone

- 100% absorbed; F = 80%
- 90% bound; V = 1 L / kg
- $t_{1/2}$ = 4 h; Cl = 120 - 200 mL/ min
- 150 - 600 mg / d; 500 - 1500 ng / mL
- Active m-CPP metabolite
  (anxiogenic 5HT-1 agonist, $t_{1/2}$ = 6 h)
- May give with MAOIs
- CYP3A4 substrate
- Few metabolic interactions
- Low therapeutic index (sedation)

Nefazodone

- 100% absorbed (↓ with food); F = 20%
- 99% bound; V = 0.5 L / kg
- $t_{1/2}$ = 3 h; Cl = 500 - 2000 mL/ min
- 300 - 600 mg / d
- Active m-CPP metabolite

  (anxiogenic 5HT-1 agonist, $t_{1/2}$ = 6 h)
- Active hydroxy-nefazodone metabolite

  (blocks 5HT reuptake, 5HT-2, $t_{1/2}$ = 3 h)
- 3A4 inhibitor:↑ triazolam, alprazolam, carbamazepine
- 3A4 substrate; nonlinear kinetics
- Moderate therapeutic index (sedation, hepatotoxicity)

Nefazodone Interactions

Nefazodone $\rightarrow\uparrow$ Drug
Via 3A3/4

alprazolam
triazolam
carbamazepine
cyclosporin

Mirtazapine

- F = 50%; 85% bound; V = 4 L / kg
- $t_{1/2}$ = 30 h; men 26 h, women 37 h
- Cl = 500 mL / min
- 15 - 45 mg / d; 40 - 120 ng / mL
- 2D6 > 1A2 → 8-hydroxy-MIRT
  3A → N-desmethyl-MIRT, N-oxide-MIRT
- N-desmethyl-MIRT metabolite
  1/10 activity, 1/3 plasma level of MIRT
- No clinically significant enzyme inhibition
- Sedation, dizziness, ↑ weight, ↑ cholesterol
- 0.1% agranulocytosis; 2% LFTs > 3 x ULN

MAO Inhibitors *

- $t_{1/2}$ brief & not directly related to effects (irreversible MAO inhibition)
- Dose
  - Phenelzine – 45 - 90 mg / day
  - Tranylcypromine – 30 - 100 mg / day
- 85% MAO inhibition needed
- Therapeutic index
  - Phenelzine – low
  - Tranylcypromine – low-mod
- 2 week wait for SSRIs, SNRIs, bupropion
- Metabolism
  - Not fully determined
  - "Suicide" inhibition component
  - CBZ inducible?

MAO Inhibitors

SERIOUS dietary restrictions

high tyramine foods -

cheese, chianti, fava …

(give patients list)

SERIOUS drug interactions

SSRI, CMI, stimulants ...

MAO Inhibitor Interactions

Foods

high tyramine

cheese

chianti

fava

...

Drugs

decongestants

opiates

SSRIs, SNRIs, CMI

stimulants

...

nefazodone ?

bupropion ?

(Li, VPA okay)

(CBZ okay?)

Selegiline Transdermal

- F = 30% (i.e. 20 mg / 20 cm^2 = 6 mg / 24 h)
- Absorption independent of dose
- 90% bound;
- $t_{1/2}$ = 24 h; Cl = 1400 mL / min
- 6-12 mg / 24 h (dietary tyramine restricted over 6 mg / 24 h)
- No first-pass effect, metabolized by
  - N-dealkylation to N-desmethylselegiline
  - N-deproparglyation to R(-)methamphetamine
- Contraindicated (pharmacodynamic interactions)
  - Antidepressants, CBZ, OXC, opiates, sympatomimetics . . .

Anxiolytic Metabolism

*

Class / Drug	Substrate of	Inhibited by
2-Keto clorazepate diazepam flurazepam	2C19, 3A4	fluoxetine fluvoxamine
Triazolo alprazolam triazolam	3A4	fluoxetine fluvoxamine nefazodone
7-Nitro clonazepam nitrazepam	N-reduction (3A4)	-
3-Hydroxy lorazepam oxazepam temazepam	Conjugation UGTs	-

Benzodiazepines

- 100% absorbed (↓ with antacid)
- 95% bound; V = 1 L / kg
- $t_{1/2}$: short (< 6 h) triaz, cloraz, fluraz
  intermed (6-20 h) alpraz, loraz, oxaz, temaz
  long (> 20 h) diazepam, clonazepam
- Metabolites: active (2-keto, triazolo)
  inactive (3-hydroxy, 7-nitro)
- $t_{1/2}$: short (< 6 h) alpha-hydroxyalprazolam
  intermed (6-20 h) desmethylchlordiazepoxide
  long (> 20 h) desmethyldiazepam
  desalkyflurazepam
- Kinetic interactions: 2-keto (+), triazolo (+)
  7-nitro (±), 3-hydroxy (-)
- High therapeutic indices

Benzodiazepines

2-Keto	Triazolo	7-Nitro	3-Hydrox
clorazepate diazepam flurazepam	alprazolam triazolam	clonazepam nitrazepam	lorazepam oxazepam temazepam
N-dealk [2C19] - 3-hydrox [3A4]	4-hydrox [3A4], α-hydrox [3A4]	N-reduction	direct conjugation
active,long t1/2 metabs	active,short t1/2 metab (alpraz)	inactive metabs	inactive metabs
+ kinetic ints	+ kinetic ints	± kinetic ints	± kinetic ints

Benzodiazepine Interactions

Drug →↑ 2-Keto BZ
clorazepate, diazepam, flurazepam

Via 2C19, 3A3/4
fluoxetine
fluvoxamine
disulfiram
BCPs
ketoconazole
cimetidine
isoniazid
omeprazole
propranolol

Drug →↑ Triazolo BZ
alprazolam, triazolam

Via 3A3/4
fluoxetine
fluvoxamine
nefazodone
diltiazem
BCPs
ketoconazole
cimetidine
erythromycin
propoxyphene

Benzodiazepine Interactions

*

2-Keto

clorazepate, diazepam
flurazepam

N-dealkylation [2C19] → 3-hydroxylation [3A4]

↑ metabolism with:
cigs, barbiturate
rifampin

↓ metabolism with:
fluoxetine, fluvoxamine
disulfiram, isoniazid
BCPs, cimetidine
ketoconazole,omeprazole
propranolol

Triazolo

alprazolam
triazolam

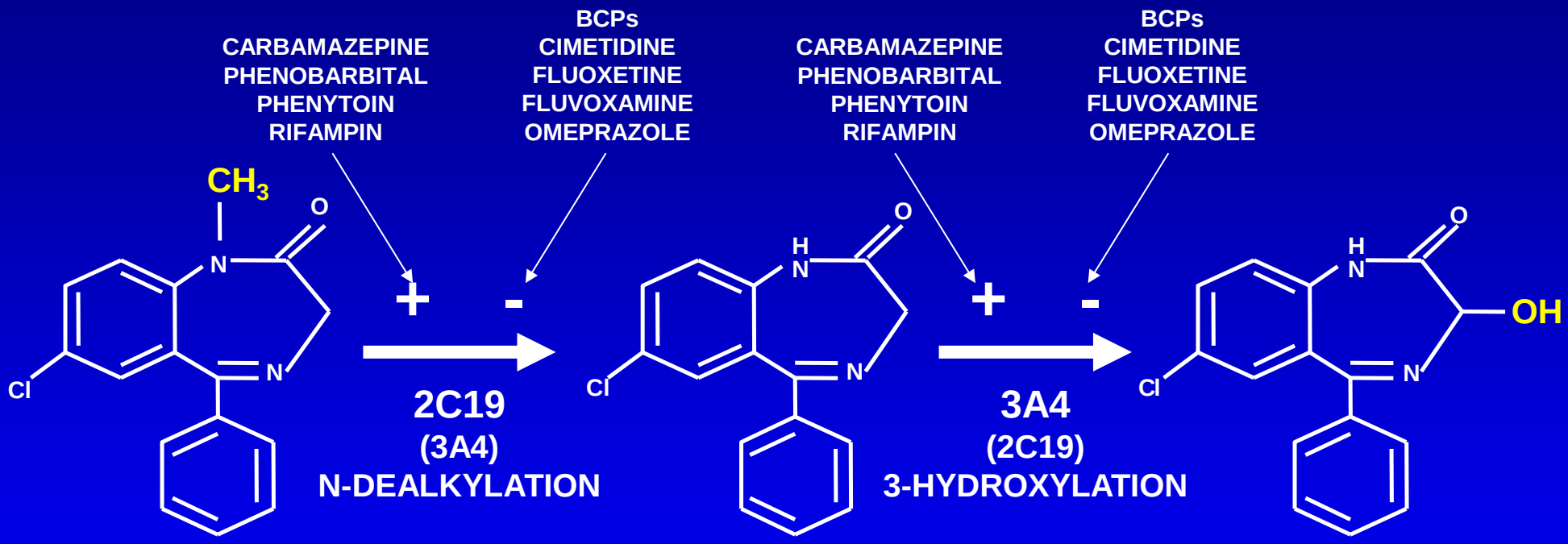
4-hydroxylation [3A4],
□-hydroxylation [3A4]

↑ metabolism with:
CBZ

↓ metabolism with:
fluoxetine, fluvoxamine
nefazodone, BCPs
erythromycin,ketoconazole
cimetidine, propoxyphene

*

Diazepam Metabolism



DIAZEPAM

ACTIVE
2-KETO-BZ

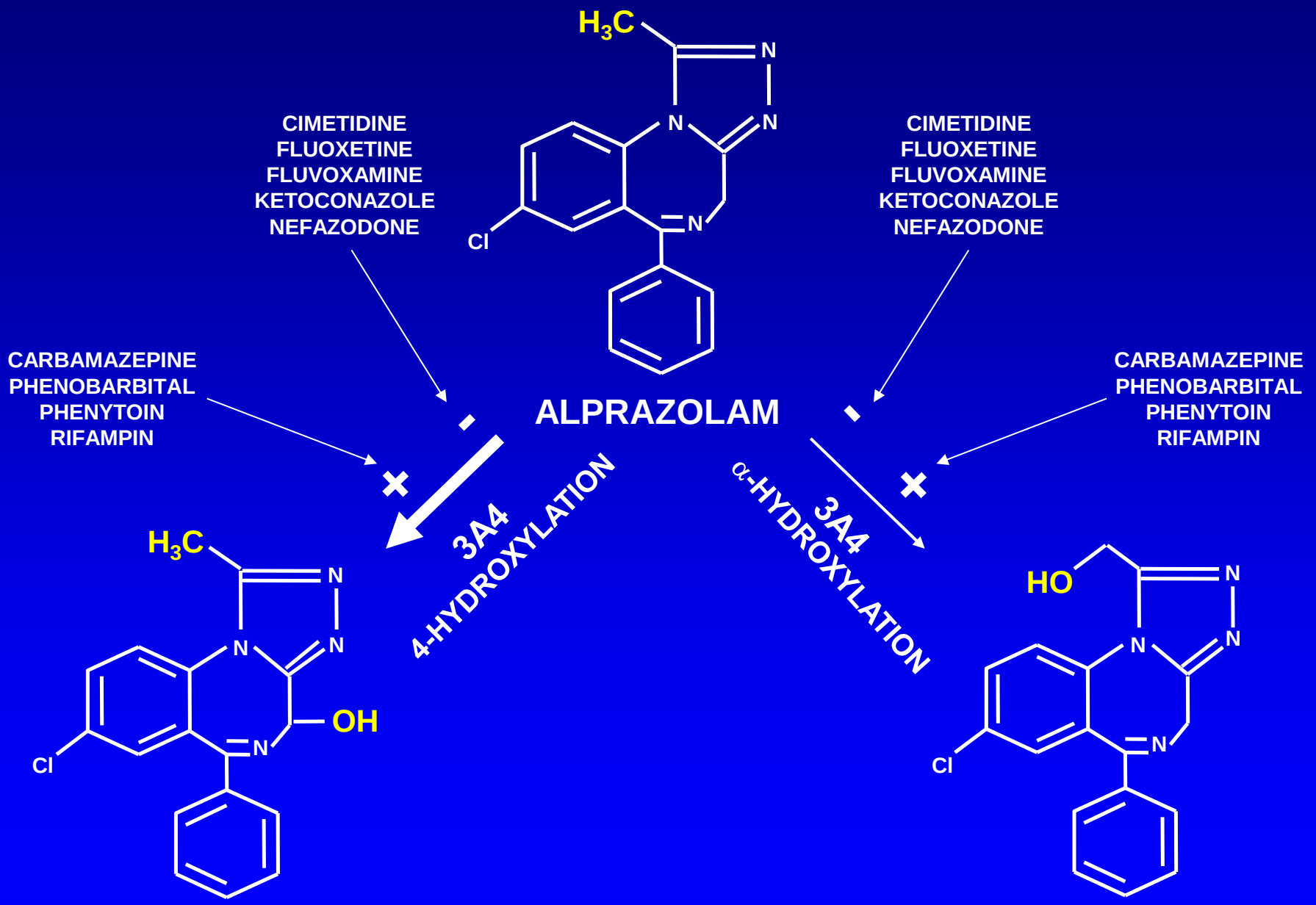
N-DESMETHYL-DIAZEPAM

ACTIVE
METABOLITE

OXAZEPAM

ACTIVE
3-HYDROXY-BZ
(DIRECTLY CONJUGATED)

Alprazolam Metabolism



Antipsychotic Metabolism

Drug	Substrate of	Inhibits
Haloperidol	2D6	2D6
Fluphenazine	2D6,+/-1A2	2D6
Perphenazine	2D6	2D6
Thioridazine	2D6	2D6
Clozapine	1A2, ± 2D6	-
Risperidone	2D6, 3A4	-
Olanzapine	UGTs,1A2	-
Ziprasidone	aldehyde ox,3A4, ± 1A2	-
Aripirazole	2D6, 3A4	-
Quetiapine	3A4	-

Typical Antipsychotics

- F = 20 - 80%
- Absorption ↓ with antacid
- 80 - 95% bound; V = 10 - 40 L / kg
- $t_{1/2}$ = 12 - 24 h; Cl = 70 - 600 mL / min
- Low potency: 200 - 600 mg / day
  High potency: 5 - 20 mg / day
- Active metabolites
  chlorpromazine 7-hydroxy-chlorpromazine
  thioridazine mesoridazine
  haloperidol reduced haloperidol loxapine
  amoxapine
- Low therapeutic index (neurotoxicity)

Typical Antipsychotic Interactions

Drug→↑AP

- tricyclics
- fluoxetine
- β blockers
- cimetidine

Drug→↓AP

- carbamazepine
- phenobarbital
- phenytoin
- cigarettes
- rifampin

AP →↑ Drug

- tricyclics

Clozapine

- 100% absorbed; F = 70%
- 97% bound; V = 5 L / kg
- $t_{1/2}$ = 12 h; Cl = 750 mL / min
- 50 - 900 mg / d; 100 - 600 ng / mL
- Desmethyclozapine metabolite (active?)
- CYP1A2 > CYP2D6 substrate or CYP3A4
- Low therapeutic index (sedation, seizures)

Clozapine Interactions

Drug →↑ CLOZ	Drug →↓ CLOZ
fluoxetine	Cigarette smoke
fluvoxamine	carbamazepine
cimetidine	phenytoin
risperidone	
± valproate	

Risperidone

- 90 - 100% absorbed; F = 70%
- 90% bound; V = 1 L / kg
- $t_{1/2}$ = 3 h; Cl = 400 mL/ min
- 4 - 16 mg / d
- 9-hydroxy-risperidone metabolite (active, $t_{1/2}$ = 23 h)
- Risperidone is CYP2D6 substrate
- Carbamazepine $\rightarrow \downarrow$ risperidone
- Fluoxetine $\rightarrow \uparrow$ risperidone
- Mod therapeutic index (neurotoxicity)

Paliperidone *

- 9-hydroxy metabolite of risperidone
- 28% absorbed (increased 54-60% by food)
- Cmax = 24 h (OROS sustained release formulation)
- 74% bound; V = 7 L / kg; $t_{1/2}$ = 23 h
- 6 mg / d recommended dose (range 3-12 mg / d)
- Linear kinetics from 3 to 12 mg
- 59% excreted unchanged in urine
- 4 minor (< 10%) metabolic pathways
- ↓ Clearance / ↑ $t_{1/2}$ / ↑ exposure with renal impairment
  - ↓32% / 24 h / ↑1.5 fold - in mild (CrCl 50-80 mL/min)
  - ↓64% / 40 h / ↑2.6 fold - in moderate (CrCl 30-50 mL/min)
  - ↓71% / 51 h /↑4.8 fold - in severe (CrCl 10-30 mL/min)

Olanzapine

*

- Well absorbed
- 93% bound; V = 15 L / kg
- $t_{1/2}$ = 30 h; Cl = 400 mL / min
- 5 - 20 mg / d
- Substrate of UGTs and CYP1A2
- Metabolites (inactive)
  - N-glucuronide
  - N-desmethyl-olanzapine (via CYP1A2)
- CBZ, smoking $\rightarrow\downarrow$ olanzapine
- Fluvoxamine $\rightarrow\uparrow$ olanzapine

Quetiapine *

- 100% absorbed; F = 100%
- 83% bound; V = 10 L / kg
- $t_{1/2}$ = 6 h; Cl ↓ 40% in elderly
- 50 - 800 mg / d (in divided doses)
- Norquetiapine - active CYP3A4 metabolite (12 h $t_{1/2}$)
- Sulfoxide - inactive CYP3A4 metabolite
- PHT, thioridazine → ↓ quetiapine
- Quetiapine →↑ warfarin
- Well tolerated with lithium
- No effect on lithium levels

Ziprasidone *

- 60% absorbed with food (30% unfed)
- 99% bound; V = 1.5 L / kg
- $t_{1/2}$ = 6.6 h; Cl = 525 mL / min
- 40 - 160 mg / day p.o.; 20 - 40 mg / day i.m.
  (in 2 divided doses with food)
- Metabolism
  - 2/3 aldehyde oxidase reduction
  - 1/3 P450 oxidation (CYP3A4)
- S-methyl-dihydro-ziprasidone metabolite (active?)
- carbamazepine → ± ↓ ziprasidone
- ketoconazole → ↑ ziprasidone
- No effect on lithium or BCP levels

Aripiprazole

- F = 87%
- 99% bound; V = 4.9 L / kg
- $t_{1/2}$ = 75 h
- 10 - 30 mg / day
- Metabolized by CYP2D6, CYP3A4
- Active dehydro-aripiprazole metabolite ($t_{1/2}$ = 94 h)
- carbamazepine → ↓ aripiprazole
- ketoconazole → ↑ aripiprazole
- quinidine (fluoxetine?, paroxetine?) → ↑ aripiprazole
- Not affected by lithium or VPA

Asenapine

*

- F = 35% sublingual (< 2% oral – first pass effect)
- 95% bound; V = 20 L / kg
- $t_{1/2}$ = 24 h
- 5 – 10 mg bid; sublinear kinetics
- Avoid eating/drinking for 10 minutes after taking
- Metabolized by UGT1A4, CYP1A2 > 3A4, 2D6
- Tobacco smoking does not alter kinetics
- Weak CYP2D6 inhibitor
- Not recommended if severe hepatic impairment
- asenapine → ↑ paroxetine; fluvoxamine → ↑ asenapine
- Avoid combining with other drugs that increase QTc

Iloperidone

*

- F = 96%
- 95% bound; V = 20 - 40 L / kg
- $t_{1/2}$ = 18/33 h (CYP2D6 extensive/poor metabolizers)
- Start 1 mg bid, increase by 1 mg bid to 6 - 12 mg bid (initial titration to reduce orthostasis risk)
- Metabolized by carbonyl reduction, CYP2D6, CYP3A4
- Supralinear kinetics
- Active P88 metabolite ($t_{1/2}$ = 26/37 h)
- ketoconazole → ↑ iloperidone
- fluoxetine, paroxetine → ↑ iloperidone
- Avoid combining with other drugs that increase QTc

Lurasidone

*

- F = 9-19%; linear kinetics
- 99% bound; V = 90 L / kg; $t_{1/2}$ = 18 h
- Start 20 mg with dinner, may increase to 120 mg
- Metabolized by CYP3A4; ID-14283 active metabolite
- Food (≥ 350 calories) doubles absorption
- ≤ 40 mg/day if mod/severe hepatic/renal impairment
- ketoconazole → ↑ lurasidone
- rifampin → ↓ lurasidone
- No sig interactions with lithium, valproate or BCPs
- Avoid with strong CYP3A4 inducers/inhibitors

Cariprazine

- F = “high”; linear kinetics; $t_{1/2}$ = 5 days
- Active didesmethyl-CARI metabolite ($t_{1/2}$ = 3 weeks)
- Metabolized by CYP3A4 > CYP2D6
- Weakly inhibits CYP3A4 & CYP2D6

Anticonvulsant Elimination

Drug	Substrate of	Induces / Inhibits
Carbamazepine	3A4	induces 3A4, UGTs
Valproate	conj>□-oxid>P450oxid	weak inhibitor
Felbamate	renal>conj,oxid	induces 3A4
Gabapentin	renal excretion	-
Lamotrigine	conjugation	Weak inducer UGTs
Topiramate	renal>hydrox,hydrol,conj	± inhibits 2C19, induces 3A4
Tiagabine	3A4, conjugation	-
Oxcarbazepine	reduction	induces 3A4
Vigabatrin	renal excretion	-
Zonisamide	3A4 (reduction)	-

Gabapentin

- F = 60%
- Absorption less with doses > 900 mg
- 0% bound; V = 1 L / kg
- $t_{1/2}$ = 6 h; Cl = 120 mL / min = GFR
- 900 - 4800 mg / d; > 2 mg/mL
- Excreted unchanged in urine
- No metabolic drug interactions
- Clearance increased with exercise (Borchert 96)
- Does not alter Li kinetics (Frye 98)

Topiramate

- F = 80%; 15% bound; V = 0.8 L / kg
- $t_{1/2}$ = 24 h; Cl = 25 mL / min
- 70% excreted unchanged monoRx 50% excreted unchanged with inducers
- Inactive hydroxylation, hydrolysis & conjugation metabolites
- 25 mg/d $\rightarrow\uparrow$ 25 mg/d q wk $\rightarrow$ 200 - 400 mg/d
- CBZ, PHT $\rightarrow\downarrow$ TPM
- TPM $\rightarrow \pm \uparrow$ PHT (inhibits CYP2C19 in vitro)
- TPM $\rightarrow \pm \downarrow$ hormonal contraceptives

Tiagabine

- F = 90%; 96% bound
- $t_{1/2}$ = 8 h with monoRx$t_{1/2}$ = 4 h with inducers
- Cl = 109 mL / min
- TGB is a CYP3A4 substrate
- Inactive 5-oxo-tiagabine & glucuronide metabolites
- 4 mg/day $\rightarrow\uparrow$ 4 - 8 mg/day q wk $\rightarrow$ up to 56 mg/day
- CBZ, PHT, PB $\rightarrow\downarrow$ TGB; VPA $\rightarrow\uparrow$ free TGB
- TGB $\rightarrow \pm \downarrow$ VPA (10%)

Oxcarbazepine

*

- 100% absorption
- MHD 40% bound; MHD V = 0.7 L / kg
- OXC $t_{1/2}$ = 2 h; MHD $t_{1/2}$ = 9 h;
- 900 - 2400 mg / day; 10 - 35 mcg / mL
- Metabolized by cytosol reductase
- Active 10-monohydroxyderivative (MHD)
- Fewer interactions than CBZ
  - No autoinduction, less heteroinduction
- OXC $\rightarrow \downarrow$ ethinyl estradiol (CYP3A4 modest induction)
- OXC $\rightarrow \uparrow$ PHT (CYP2C19 inhibition)
- Low therapeutic index (neurotoxicity)

Zonisamide

- 15% bound
- $t_{1/2}$ = 60 h with monoRx

  $t_{1/2}$ = 30 h with inducers
- Cl = 20 mL / min
- Reduced to 2-sulfamoylacetylphenol (SMAP)
- 100 mg/d → ↑ 100 mg/d q 2wks -up to 300-600 mg/d
- CBZ, PHT, PB → ↓ ZNS; LTG → ↑ ZNS

Levetiracetam

- F = 100%, < 10% bound
- 66% excreted unchanged
- 24% hydrolyzed to inactive metabolite (ucb L057)
- $t_{1/2}$ = 8 h
- Cl = 40 mL / min
- 1000 mg/d → ↑ 1000 mg/d q 2wks -up to 3000 mg/d
- CBZ, PHT, PB, VPA do not alter levels

Pregabalin

- F = 90%
- Absorption independent of dose
- 0% bound; V = 0.5 L / kg
- $t_{1/2}$ = 6 h; Cl = 80 mL / min - varies with CLcr
- 75 - 600 mg / d
- Excreted unchanged in urine
- No metabolic drug interactions

Rufinimide (Banzel™)

- F ≤ 85% (slow, ↓'s as dose ↑'s, ↑ 34% with food)
- 34% bound; V = 0.7 L / kg (at 3,200 mg/d)
- $t_{1/2}$ = 6-10 h; 1,600 – 3,200 mg / d
- Hydrolysis by carboxylesterases (not CYPs)
- Weak CYP2E1 inhibitor, weak CYP3A4 inducer
- Renal impairment: no dose adjustment
- Hepatic impairment: Caution (mild/mod); Avoid (severe)
- PB, PHT → ↓ RFN; VPA → ↑ RFN; RFN → ↓ BCPs

Lacosamide (Vimpat™)

- F = 100%
- < 15% bound; V = 0.6 L / kg
- $t_{1/2}$ = 13 h; 200 – 400 mg / d
- Metabolized by CYP3A4, CYP2C9, and CYP2C19
- Renal impairment: ↓ dose (severe)
- Hepatic impairment: ↓ dose (mild/mod); Avoid (severe)
- ↓ dose with strong CYP3A4, CYP2C9 inhibitors

Vigabatrin (Sabril™)

- F = 100%
- 0% bound; V = 1.1 L / kg
- $t_{1/2}$ = 10.5 h ; Cl - varies with CLcr
- 1,500 – 3,000 mg / d
- Excreted unchanged in urine
- Induces CYP2C9 (VGB → ± ↓ PHT)
- Renal impairment: ↓ dose
- Hepatic impairment: ?? (not metabolized)
- <u>Boxed warning</u>: Vision Loss

Esogabine (AKA Retigabine, Potiga™)

- F = 60%; V = 2-3 L / kg
- Active N-Acetyl-Metabolite (NAMR) via N-Acetyl-transferase (not CYPs)
- Binding = 80% (ESO), 45% (NAMR)
- $t_{1/2}$ = 7-11 h; Cl = 700 mL / min
- 600 – 1,200 mg / d
- Renal impairment: ↓ dose (mod/severe)
- Hepatic impairment: ↓ dose (mod/severe)
- CBZ, PHT → ↓ ESO; NAMR → ↑ Digoxin
- Warning: confusion, psychosis, hallucinations
- Boxed warning: Retinal Abnormalities and Potential Vision Loss

Clobazam (Onfi™)

- F = 100%; V = 1.4 L / kg
- Pro-drug (CYP3A4) for N-desmethyl-CLB (N-DM-CLB)
- N-DM-CLB metabolized by CYP2C19
- Binding = 80-90% (CLB), 70% (N-DM-CLB)
- $t_{1/2}$ = 36-42 h (CLB), 71-82 h (N-DM-CLB)
- 20 – 40 mg / d (after titration)
- Renal impairment: = dose (mild/mod); ???(severe)
- Hepatic impairment: ↓ dose (mild/mod); avoid (severe)
- CYP2D6 inhibitor; weak CYP3A4 inducer
- CLB → ↑ CYP2D6 substrates, ± ↓ BCPs; Etoh → ↑ CLB
- CYP2C19 inhibitors → ↑ N-DM-CLB

Perampanel (Fycompa™)

- F = 100%
- 95% bound; $t_{1/2}$ = 105 h; Cl = 12 mL / min
- 4 – 8 mg / d (higher if induced)
- Metabolized by CYP3A4/5, then conjugated
- Hepatic impairment: ↓ dose (mild/mod); avoid (severe)
- CBZ, PHT, OXC, ± PB, ± PRIM → ↓ PMP
- PMP → ↓ BCPs
- Boxed warning: Serious Psychiatric & Behavioral Reactions (aggression, hostility, irritability, anger, homicidal ideation)

Eslicarbazepine Acetate (Aptiom™)

- L-isomer of OXC metabolite
- F = > 90%; < 40% bound; V = 0.9 L / kg
- $t_{1/2}$ = 13-20 h; Cl = 20 mL / min
- ↓ dose in moderate/severe renal impairment
- Avoid in severe hepatic impairment
- 400 – 1,200 mg / d
- First-pass hydrolysis to ESL, then congugated
- Inhibits CTP2C19; induces CYP3A4
- CBZ, PHT, PB, PRIM → ↓ ESL
- ESL → ↑ PHT; ↓ BCPs, statins, warfarin; ±↓ CBZ

Calcium Channel Blockers *

- 90 - 100% absorbed; F = 10 - 50%
- 80 - 90% bound; V = 1 - 5 L / kg
- $t_{1/2}$ = 1 - 6 h; Cl = 70 - 140 mL / min
- Verapamil (phenylalkylamine) 120 - 480 mg / day
  - Diltiazem (benzothiazepine) 120 - 480 mg / day
  - Nimodipine (dihydropyridine) 60 - 360 mg / day
  - Isradipine (dihydropyridine) 5 - 20 mg / day
- Active norverapamil metabolite ($t_{1/2}$ = 10 h)
- 3A4 substrates (metabolism ↓ with cimetidine)
- verapamil, diltiazem (not dihydropyridines)
  - 3A4 inhibitors (↓ cyclosporin, CBZ metab)
- Varying therapeutic indices (cardiovascular)

Antihistamine Interactions

Antihistamines Metabolized Via 3A3/4

loratadine (Claritin)

cetirizine (Zyrtec)

fexofenadine (Allegra)

Drug →↑ Antihistamine Via 3A3/4

ketoconazole

itraconazole

fluconazole

erythromycin

clarithromycin

troleandomycin

nefazodone ?

fluvoxamine ?

Psychopharmacological Pharmacokinetics Top Ten

1. CYP3A4 – Most common P450 pathway
2. Half-life – clinically relevant concept
3. Carbamazepine – drug interactions
4. Carbamazepine – enzyme inducer
5. Valproate – enzyme inhibitor
6. Ziprasidone/Lurasidone/Vilazodone – food effects
7. Alprazolam – short half-life
8. Fluoxetine/Aripiprazole – long half-life
9. Lithium – renal excretion
10. Fluvoxamine – arcane inhibitor

Conclusions

- Combination Rx often needed
- Extensive observational clinical data
- Evolving characterization of substrates, inhibitors & inducers
- Understanding of drug metabolism
- Prediction of drug interactions

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Post Lecture Exam Question 1

1. Key pharmacokinetic parameters include: (choose one)

A. Volume of distribution (V)
B. Half life ($t_{1/2}$)
C. Clearance (Cl)
D. Therapeutic index
E. All of the above
F. A, B, and C

Question 2

2. After discontinuation, how long does it take to completely clear a drug? (choose one)

A. Clearance x half-life
B. 2 x half-life
C. 5 x half-life
D. Volume of distribution x clearance

Question 3

3. The two most important cytochrome P450 isoforms mediating drug interactions in psychiatric patients receiving combination therapies are: (choose two)

A. 1A2
B. 2C9/10
C. 2C19
D. 2D6
E. 2E1
F. 3A3/4

Question 4

4. Which of the following drugs is NOT an enzyme inducer? (choose one)

A. Carbamazepine
B. Valproate
C. Oxcarbazepine
D. Phenytoin
E. Phenobarbital
F. Primidone

Question 5

5. Which of the following drugs decrease plasma concentrations of hormonal contraceptives? (choose one)

A. Carbamazepine
B. Oxcarbazepine
C. Topiramate
D. Phenytoin
E. Phenobarbital
F. All of the above

Question 6

6. Which of the following drugs is NOT an enzyme inhibitor? (choose one)

A. Lithium
B. Bupropion
C. Fluoxetine
D. Valproate
E. Cimetidine
F. Erythromycin

Question 7

7. Which of the following drugs robustly increases plasma concentrations of lamotrigine? (choose one)

A. Carbamazepine
B. Valproate
C. Cimetidine
D. Gabapentin
E. Phenytoin

Question 8

8. Which of the following drugs have almost exclusively renal excretion? (choose one)

A. Gabapentin
B. Valproate
C. Lithium
D. Carbamazepine
E. A and C

Question 9

9. Monoamine oxidase inhibitor combination therapy is limited by:

A. Side effects (low to low-moderate therapeutic index)
B. Serious pharmacodynamic drug interactions
C. Allergic reactions (rashes)
D. Their exclusively renal excretion
E. A and B
F. None of the above

Question 10

10. Which of the following benzodiazepines has least potential for drug interactions?

A. Diazepam (a 2-keto-benzodiazepine)
B. Alprazolam (a triazolo-benzodiazepine)
C. Flurazepam (a 2-keto-benzodiazepine)
D. Lorazepam (a 3-hydroxy-benzodiazepine)

Answers to Pre & Post Competency Exams

1. F
2. C
3. D & F
4. B
5. F
6. A
7. B
8. E
9. E
10. D