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 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)

Outline

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- **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

- **Bioavailability = % reaching circulation as compared to IV (F = absorption - first pass metabolism)**
- **Affected by food**
  (↑ sertraline, ziprasidone; ↓ nefazodone absorption)
- **Affected by enteric/hepatic metabolism**
  (tyramine - MAO; terfenadine - CYP3A4)
- **Speed affected by enteric motility**
  (↑ with metoclopramide, ↓ with TCAs)
- **Speed affected by 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

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

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PHASE I - Introduce functional groups

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

PHASE II - Form polar derivatives-CONJUGATION

- **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 cf CBZ)
  - Different (m-CPP anxiogenic cf 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 relationships
Tolerance	↓ therapeutic or adverse responses 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)

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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

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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

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

CYP3A4,5,7

SUBSTRATES	INHIBITORS	INDUCERS
± citalopram		CBZ
± mirtazapine	fluvoxamine	phenobarbital
nefazodone		phenytoin
reboxetine	nefazodone	
sertraline		
3° tricyclics	diltiazem	
(demethylation)	verapamil	
alprazolam		
diazepam		
midazolam		
triazolam		
buspirone		
CBZ		
Ca blockers	cimetidine	dexamethasone
H1 blockers	imidazoles	rifampin
local anesthetics	macrolides	
macrolides	naringenin	
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)

Auto. recessive; 5-10% whites, Asians 1%

Substrates: 2° & 3° TCAs, duloxetine, parox, venla, ± fluox, 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)

Auto. 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.	(= ↓)	↓	(= ↓)

MOOD STABILIZER AND ANTICONVULSANT METABOLISM

DRUG	SUBSTRATE OF	INDUCES / INHIBITS
lithium	renal excretion	-
carbamazepine	3A4, 3A5-7	induces 3A4,5,7 ...
valproate	conjugation	weak inhibitor
	β-hydroxylation	
	P450 oxidation	
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

LITHIUM CLEARANCE

Decreased by:	Not changed by:	Increased by:
thiazides	amiloride furosemide	acetazolamide mannitol
NSAIDs	ASA sulindac	aminophylline caffeine
ACE inhibitors		theophylline
dehydration elderly renal disease		pregnancy mania

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 (+)

CBZ

ACTIVE
PARENT
DRUG

\+

CYP3A3/4

\-

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

CBZ-E

ACTIVE
EPOXIDE
METABOLITE

\+

EPOXIDE
HYDROLASE

\-

↑ CBZ-E LEVELS WITH
lamotrigine (-?)
progabide (-)
VALPROATE (-)
VALPROMIDE (--)

CBZ-D

INACTIVE
DIOL
METABOLITE

* molecular bichemical evidence supports CYP3A3/4

Ketter TA, et al: J Clin Psychopharmacol 1991;11:198-203,306-312

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.

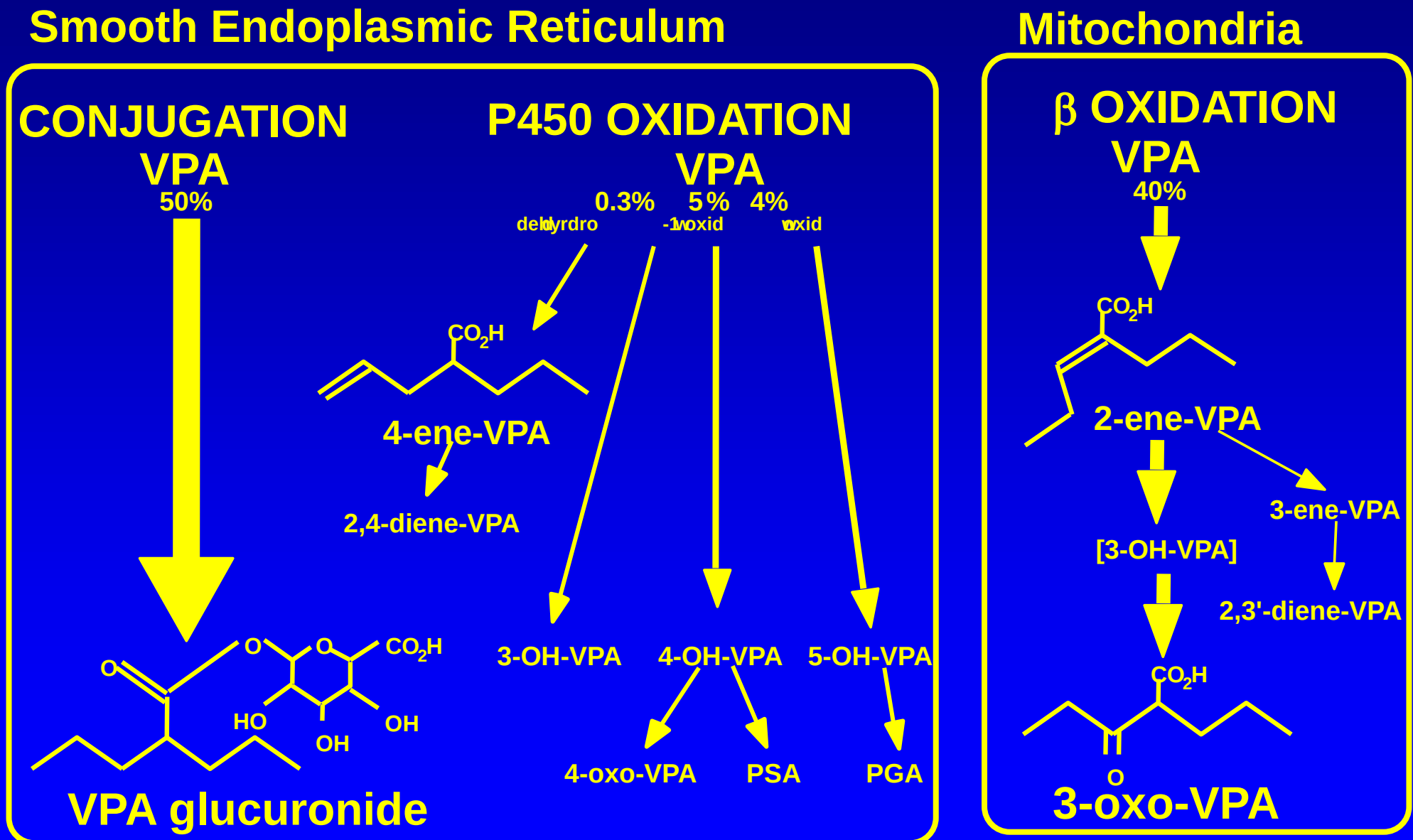
CYP3A4-MEDIATED CBZ DRUG INTERACTIONS

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.

VPA-PLASMA PROTEIN BINDING INTERACTIONS

VPA $\rightarrow\uparrow$ **FREE DRUG**

CBZ
diazepam
phenytoin
tiagabine
tolbutamide
warfarin

DRUG $\rightarrow\uparrow$ **FREE VPA**

ASA
NSAIDs

DVPX 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)

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

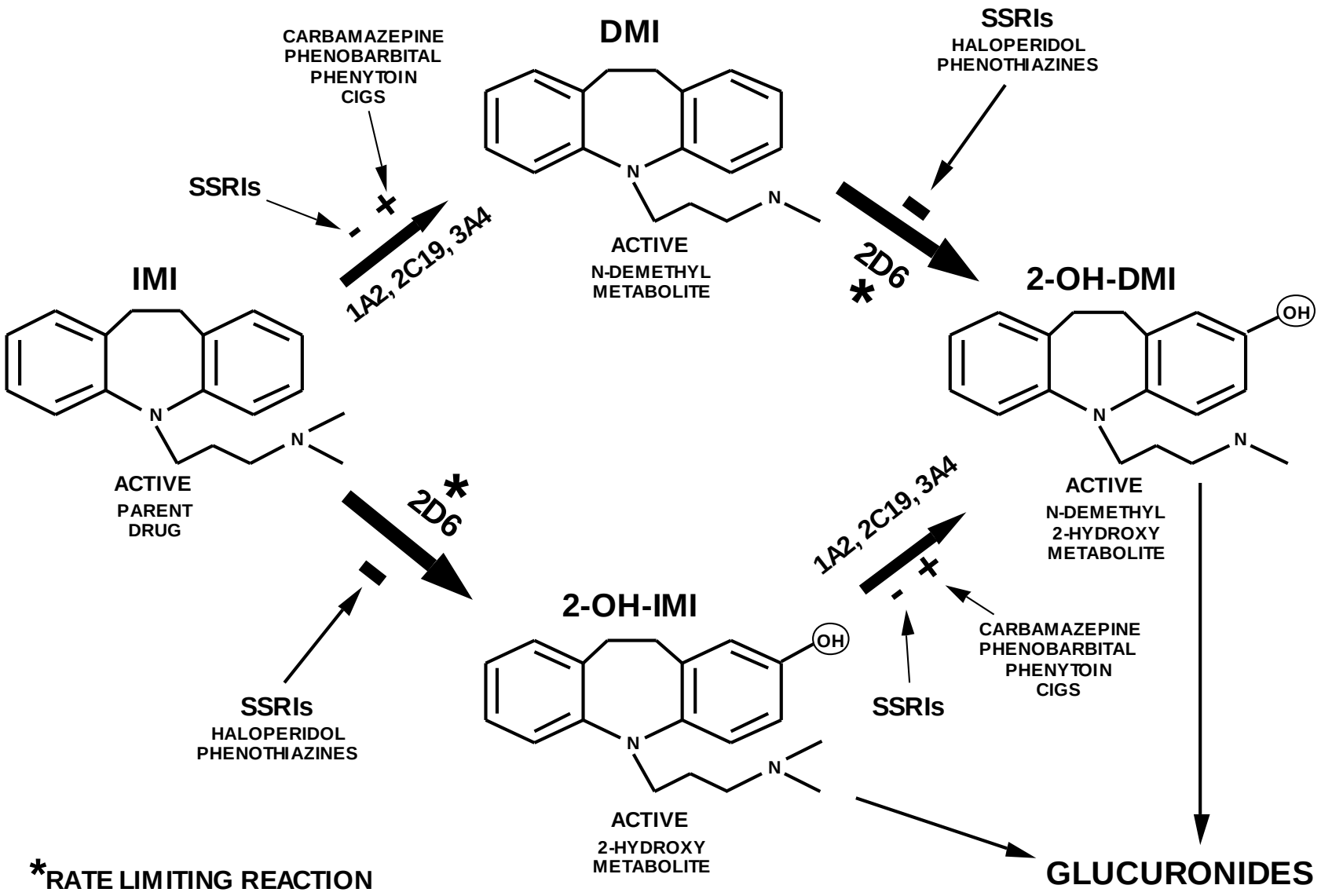
DRUG →↑ TCA

VIA 2D6	VIA ?
fluoxetine	methylphenidate(?)
± sertraline	disulfiram
paroxetine	acute ethanol
haloperidol	valproate (?)
phenothiazines	azole antifungals (?)
methadone	BCPs (?)
propafenone	cimetidine
quinidine	chloramphenicol

TRICYCLIC INTERACTIONS

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

IMIPRAMINE METABOLISM



*RATE LIMITING REACTION

SSRIs & SNRIs

- SSRIs - fluoxetine, sertraline, paroxetine, fluvoxamine
- SNRI - duloxetine, venlafaxine
- ↓ side effects, ↑ therapeutic index cf 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- substrate of CYP1A2 and CYP2D6 and modest inhibitor CYP2D6

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 ↑ 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 200mg/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 - 60 mg / d
- Demethylcitalopram metabolite (± active, via 2C19, 3A4, ± 2D6)
- Didemethylcitalopram metabolite (± active, via 2D6)
- Contraindicated-canine acral lick syndrome
- 2 week wait for MAOIs
- Weak 1A2, 2C19, 2D6 inhibitor
- High therapeutic index

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 / d
- S-Demethylcitalopram metabolite (± active, via 2C19, 3A4, ± 2D6)
- S-Didemethylcitalopram metabolite (± active, via 2D6)
- Decreased clearance with hepatic impairment
- Contraindicated-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 / d
- Desmethylvenlafaxine metabolite (active, $t_{1/2}$ = 11 h)
- 2 week wait for MAOIs
- CYP2D6 substrate
- Modest inhibition on 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

*

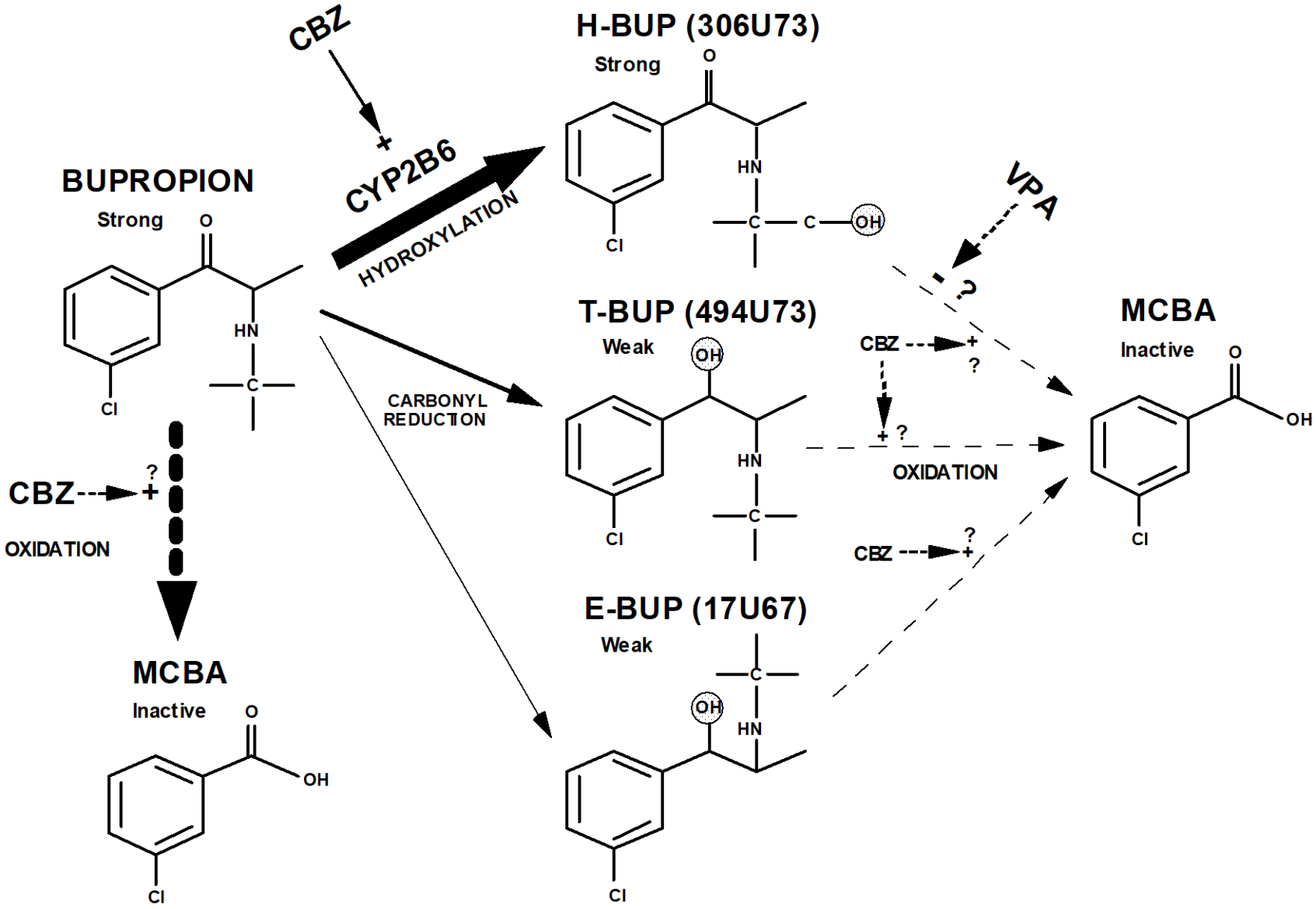
PHARMACOKINETICS OF SELECTED SSRIs AND SNRIs

	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 / d; > 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 →↑ DRUG

VIA 3A3/4
alprazolam
triazolam
carbamazepine
cyclosporin

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 ?

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 $\rightarrow$ 8-hydroxy-MIRT
  3A $\rightarrow$ 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
  - Tranylcypromine - 30 - 100 mg / d
- 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	DRUGS
high tyramine	decongestants
cheese	opiates
chianti	SSRIs, SNRIs, CMI
fava	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

BZ 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

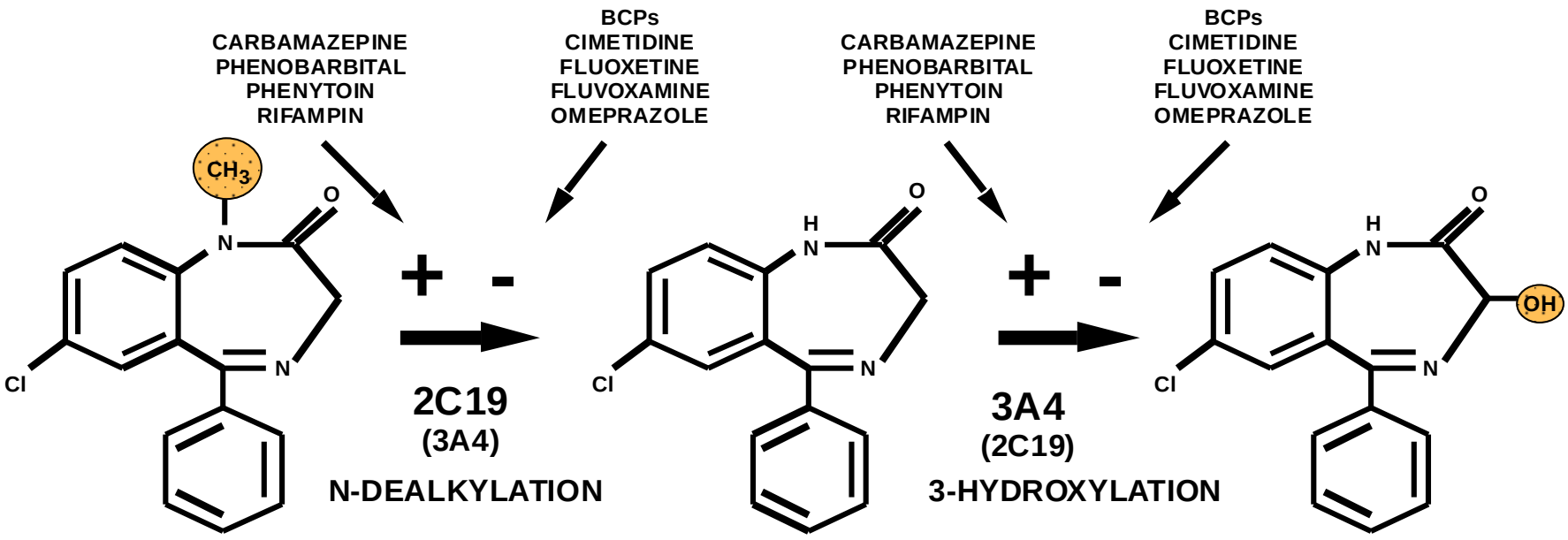
alprazolam
triazolam

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

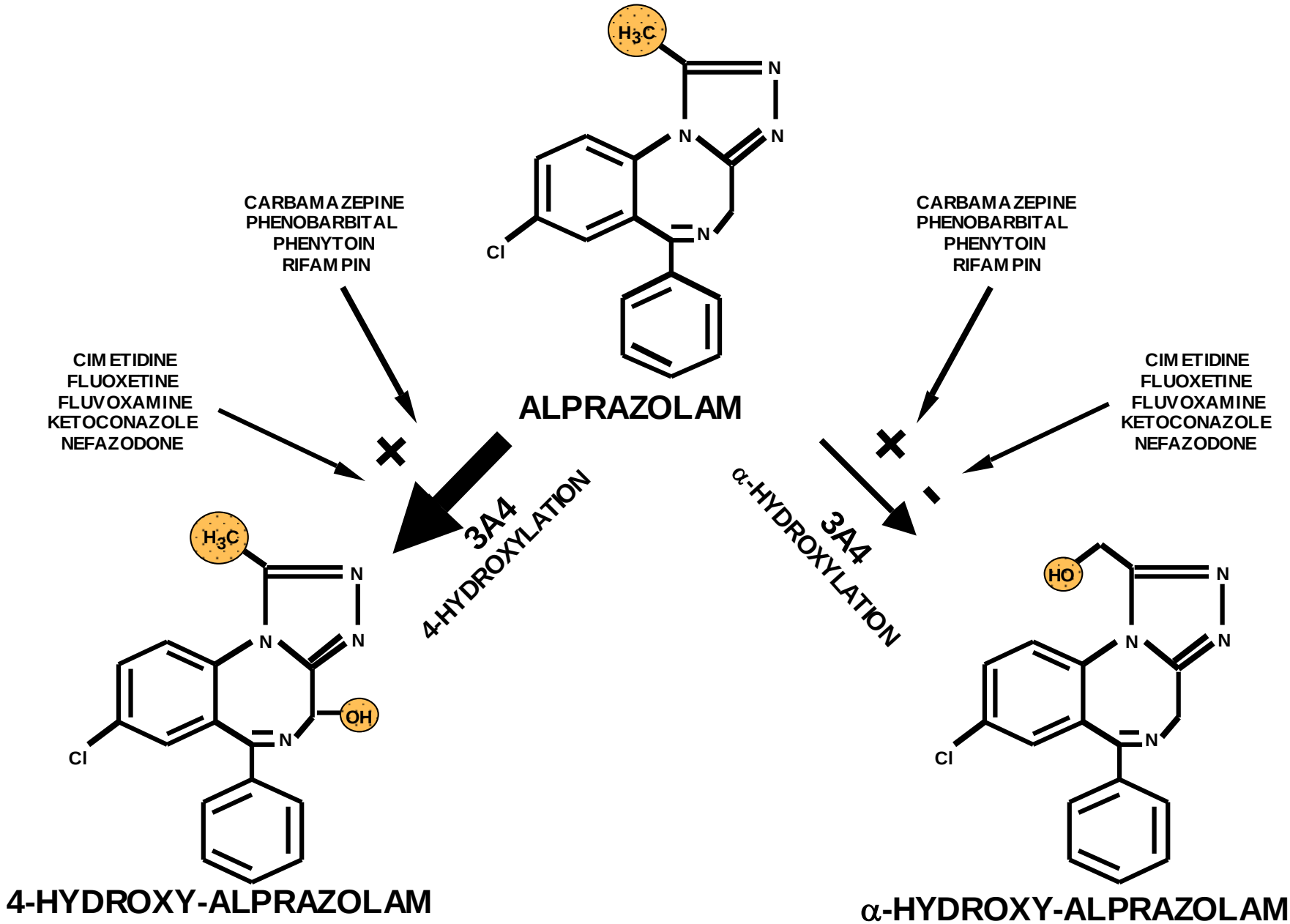
N-DESMETHYL-DIAZEPAM

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 / d
  High potency: 5 - 20 mg / d
- Active metabolites
  chlorpromazine 7-hydroxy-CPZ
  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
- t1/2 = 6.6 h; Cl = 525 mL / min
- 40 - 160 mg / d p.o.; 20 - 40 mg / d 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
- t1/2 = 75 h
- 10 - 30 mg / d
- Metabolized by CYP2D6, CYP3A4
- Active dehydro-aripiprazole metabolite (t1/2 = 94 h)
- carbamazepine → ↓ aripiprazole
- ketoconazole → ↑ aripiprazole
- quinidine → ↑ aripiprazole
- Not affected by lithium or VPA

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/d $\rightarrow\uparrow$ 4 - 8 mg/d q wk $\rightarrow$ up to 56 mg/d
- 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 / d; 10 - 35 mcg / mL
- Metabolized by cytosol reductase
- Active 10-monohydroxyderivative (MHD)
- Fewer interactions than CBZ
  - No autoinduction, less heteroinduction
- OXC → ↓ ethinyl estradiol (CYP3A4 modest induction)
- OXC → ↑ 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 $\rightarrow \uparrow$ 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

Ca 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 / d
  - diltiazem (benzothiazepine) 120 - 480 mg / d
  - nimodipine (dihydropyridine) 60 - 360 mg / d
  - isradipine (dihydropyridine) 5 - 20 mg / d
- 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)

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