Pharmacokinetics of Psychotropic Drugs

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Pre-Lecture Exam Question 1

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

A. Volume of distribution (V)
B. Half life (t1/2)
C. Clearance (C1)
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 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)

OVERVIEW

- **CONCEPTS**
  Pharmacokinetics, Pharmacodynamics
- **CYTOCHROME P450**
  Isoforms, Substrates, Inhibitors, Inducers
- **MOOD STABILIZERS**
  Li, CBZ, VPA
- **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)
(Load with V x [desired conc. change])	Loading dose
$t_{1/2}$ (half life) ($t_{1/2}$ = .7 x V / Cl)	Time to steady state = 5 x $t_{1/2}$
Cl (clearance) (C_{ss} = dose x dosing interval x F / Cl)	Steady state concentration

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 - MAOI 5 wk wait** **venlafaxine - 2 wk MAOI wait**
Cl **(clearance)**	**↑ [Li] in renal failure** **↑ [diazepam] in liver failure**

ABSORPTION

- **Bioavailability = % reaching circulation**
  (F = absorption - first pass metabolism)
- **Affected by food**
  (↑ sertraline, ↓ 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

- 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

PHASE I - Introduce functional groups

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

PHASE II - Form polar derivatives

- **Glucuronidation - oxazepam**
- **Sulfation - acetaminophen**
- **Methylation - norepinephrine**
- **Acetylation - clonazepam, phenelzine**

METABOLITES COMPARED TO PARENT DRUGS

- Longer $t_{1/2}$
- More water soluble
- Can be more active (hydroxylated, demethylated)
- Pharmacodynamics may be
  - Similar (CBZ-E cf CBZ)
  - Different (m-CPP cf trazodone)

ACTIVE METABOLITES

carbamazepine	carbamazepine-10,11-epoxide oxcarbazepine monohydroxyderivitive (MHD)
valproate	2-ene-valproate, 4-ene-valproate
amitriptyline	nortriptyline, hydroxynortiptyline
IMI/DMI	imipramine desipramine, hydroxy-IMI and DMI
amoxapine	hydroxyamoxapine
fluoxetine	norfluoxetine
sertraline	N-desmethylsetraline (±)
citalopram	di/desmethylcitalopram
venlafaxine	O-desmethylvenlafaxine
bupropion	hydroxybupropion
trazodone	m-chlorophenylpiperazine
nefazodone	m-CPP, hydroxynefazodone

ACTIVE METABOLITES

diazepam	N-desmethyldiazepam
	clorazepate N-
desmethyldiazepam	chlordiazepoxide N-
desmethyldiazepam	alprazolam apha-
hydroxyalprazolam	flurazepam
	desalkylflurazepam buspirone
	pyrimidinylpiperazine
chlorpromazine	hydroxychlorpromazine
	thioridazine mesoridazine
haloperidol	reduced haloperidol
loxapine	amoxapine
clozapine	desmethyclozapine (±)
	risperidone 9-
hydroxyrisperidone	

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)

INTERACTION POTENTIAL

- Low therapeutic index
- Long half-life
- Nonlinear kinetics
- Active metabolites
- Metabolic inhibition / induction
- Single metabolic route
- CYP2D6, CYP3A3/4

P450 NOTATION

CYP2D6

CYP - CYtochrome P450
2 - family (> 40% homology)
D - subfamily (> 55% homology)
6 - gene

KEY ISOFORMS FOR DRUG METABOLISM

ISOFORM	SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	TCAs,cloz,olanz	fluvoxamine	cigs,omep
CYP2C9/10	phenytoin,THC	fluvoxamine	rifam,barb
CYP2C19	BZs,TCAs	fluox,fluvox	rifampin
CYP2D6	TCAs,parox,mirtaz venla, ±fluox	parox,fluox ±fluvox, ±sertra disulfiram	- Etoh,INH
CYP2E1	Etoh		
CYP3A3/4	BZs,CBZ Sertraline Nefazodone TCAs, mirtaz Ca blockers→	fluoxetine fluvoxamine nefazodone diltiazem verapamil	CBZ phenytoin phenobarb rifampin

CYP2D6

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

CYP3A3/4

SUBSTRATES	INHIBITORS	INDUCERS
± citalopram	fluoxetine	CBZ
± mirtazapine	Fluvoxamine	phenobarbital
Nefazodone	norfluoxetine	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	troglitazone
macrolides	naringenin	
Quinidine		
steroids		

INHIBITION PROFILES

POTENCY	CYP2D6	CYP3A3/4
highest	quinidine paroxetine fluoxetine	ketoconazole erythromycin nefazodone fluvoxamine
intermediate	sertraline	fluoxetine
lowest	fluvoxamine nefazodone venlafaxine erythromycin ketoconazole	sertraline desmethyl sertraline paroxetine venlafaxine quinidine

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

cigarettes
chronic ethanol

isoniazid
rifampin

glutethimide
omeprazole

GENETIC POLYMORPHISMS

CYP2D6 (Poor Metabolizers)
Auto. recessive; 7% whites, 2% blacks, Asians
Substrates: 2° & 3° TCAs, parox, venla, ± fluox
IC antiarrhythmics, β-blockers

CYP2C19 (Poor Metabolizers)
Recessive; 3% whites, 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	3A3/4	induces 3A3/4, ...
valproate	conjugation	weak inhibitor
	β-hydroxylation	
	P450 oxidation	
phenytoin	2C9/10, ± 2C19	induces 3A3/4, ...
barbiturates	2C19	induce 3A3/4, ...
lamotrigine	conjugation	-
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:

- Thiazides
- NSAIDs
- ACE inhibitors
- Dehydration
  Elderly
  Renal disease

Not changed by:

- Amiloride
  furosemide
- ASA
  sulindac

Increased by:

- Acetazolamide
- Mannitol
- Aminophylline
- Caffeine
- Theophylline
- 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 3A3/4]
- 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;11:198-203,306-314

CARBAMAZEPINE INTERACTIONS

CBZ →↓ DRUG

Alprazolam (?)
Ethosuximide
Bupropion
Amitriptyline
Clonazepam
Clozapine
Doxycycline
Fluphenazine (?)
Haloperidol
Imipramine
Methadone
Olanzapine
Quetipine (?)
Risperidone
Thiothixene (?)

Bcps
Cyclosporine (?)
Dexamethasone
Dicumarol (?)
Ethosuximide
Felbamate
Lemotrigine
Phenytoin
Primidone
Tiagabine
Valproate

Doxacurium
Doxepin
Fentanyl
Oxiracetam (?)
Pancuronium
Prednisolone
Theophylline
Vecuronium
Warfarin

DRUG →↓ CBZ

Fluoxetine
Fluvoxamine
Nefazodone
Diltiazem
Verapamil

Felbamate (CBZ-E)
Valproate (CBZ-E)

Acetazolamide
Cimetidine
Danazol
D-propoxyphene
Gemfibrozil
Isoniazid
Macrolides
Clarithromycin
Nicotinamide
Warfarin

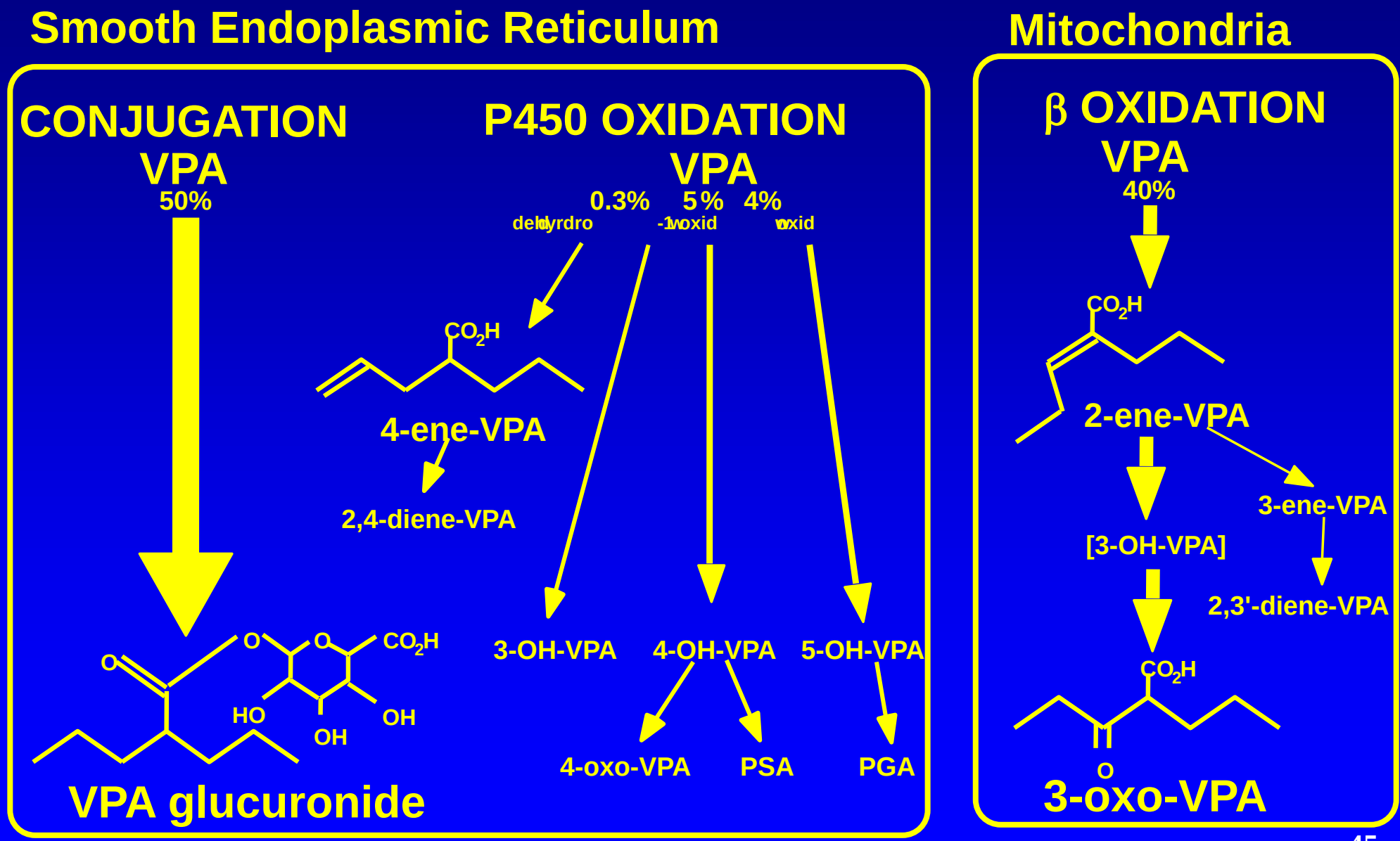
CYP3A4-MEDIATED CBZ DRUG INTERACTIONS

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 BINDING INTERACTIONS

VPA →↑ FREE DRUG

CBZ
diazepam
phenytoin
tiagabine
tolbutamide
warfarin

DRUG →↑ 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		

KEY ISOFORMS FOR ANTIDEPRESSANT METABOLISM

ISOFORM	SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	TCAs, ± mirtaz	fluvoxamine	cigs, omep
CYP2C19	± citalopram, TCAs	fluox, fluvox	rifampin
CYP2D6	± fluoxetine ± mirtazapine paroxetine venlafaxine TCAs, trazodone	bupropion fluoxetine ± fluvoxamine paroxetine ± sertraline	-
CYP3A3/4	± citalopram ± mirtazapine nefazodone reboxetine sertraline, TCAs	fluoxetine fluvoxamine nefazodone ± sertraline	CBZ phenytoin phenobarb rifampin

TRICYCLICS

- 100% absorbed; F = 20 - 70%
- 90% bound; V = 10 - 30 L / kg
- t1/2 = 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 [1A2,2C19,3A3/4]
- Low therapeutic index (anticholinergic)

TRICYCLIC INTERACTIONS

DRUG →↑ TCA

VIA 2D6

fluoxetine
± sertraline
paroxetine
haloperidol
phenothiazines
methadone
propafenone
quinidine

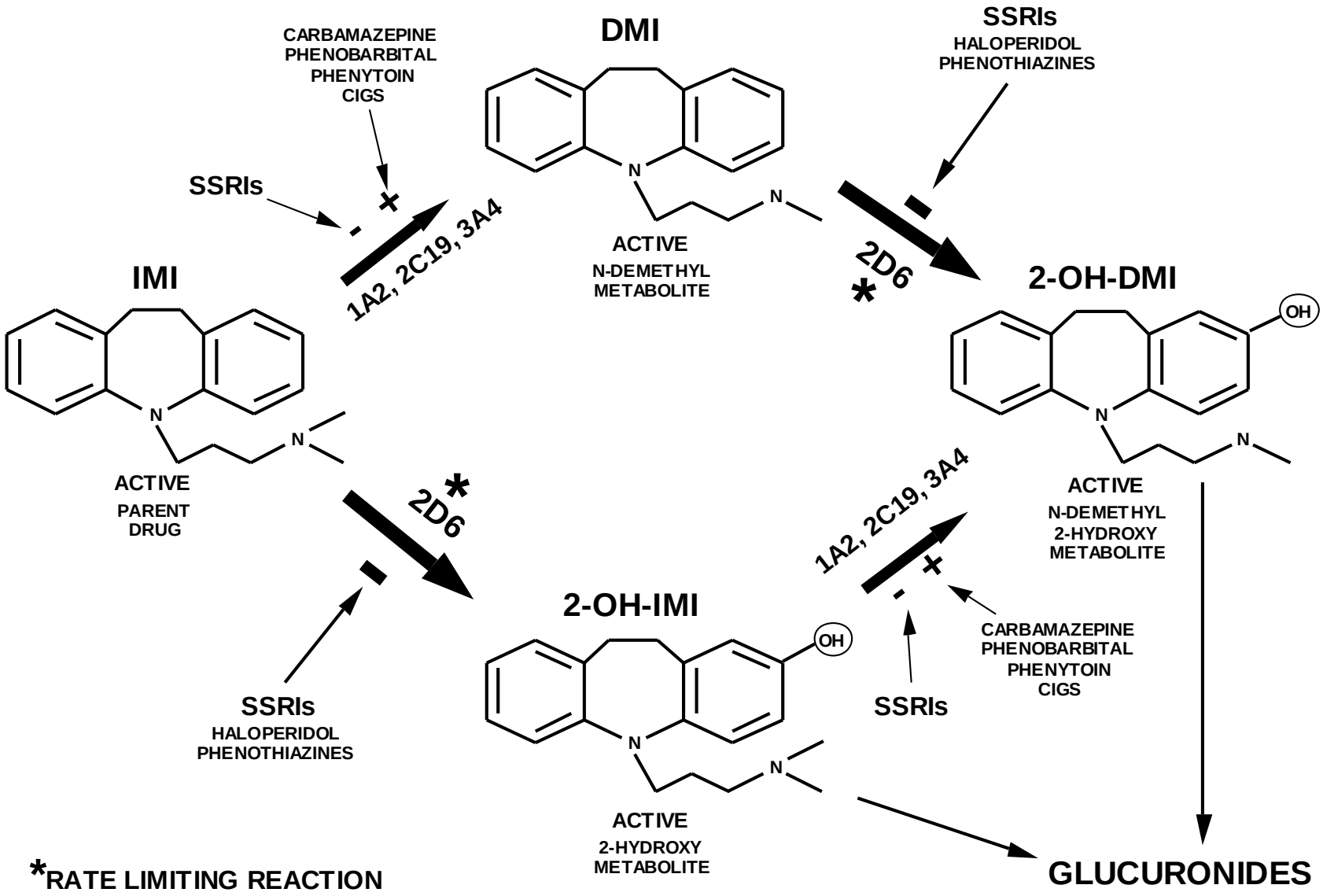
VIA ?

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

TRICYCLIC INTERACTIONS

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

IMIPRAMINE METABOLISM



*RATE LIMITING REACTION

SSRIs & SNRIs

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

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

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 d)
- 5 week wait for MAOIs
- CYP2D6 substrate (40%)
- CYP2D6 > CYP3A3/4 inhibitor
- Nonlinear kinetics (saturation)
- High therapeutic index

FLUOXETINE INTERACTIONS

FLUOXETINE →↑ DRUG

VIA 2D6
AMI, IMI
NORT, DMI
fluphenazine
haloperidol
clozapine
dextromethorphan
oxycodone

VIA 3A3/4
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

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

AMI, IMI, CMI
maprotiline
clozapine
olanzapine
methadone
caffeine
phenacetin
propranolol
theophylline

VIA 3A3/4

alprazolam
diazepam
carbamazepine
terfenadine ?
astemizole ?
cisapride ?

VIA 2C9/10

phenytoin
warfarin

VIA 2D6

haloperidol

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
- CYP3A3/4 substrate
- CYP2D6 > CYP3A3/4 inhibitor
- At 50 mg / day less effect on TCA levels than fluoxetine, paroxetine
- 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
- Minimal effects on CYP2D6, CYP3A3/4
- High therapeutic index

CITALOPRAM

- Rapidly absorbed; F = 80%
- Absorption not affected by food
- 80% bound; V = 12 L / kg
- $t_{1/2}$ = 35 h; Cl = 330 mL/ min
- 10 - 60 mg / d
- Desmethylcitalopram 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

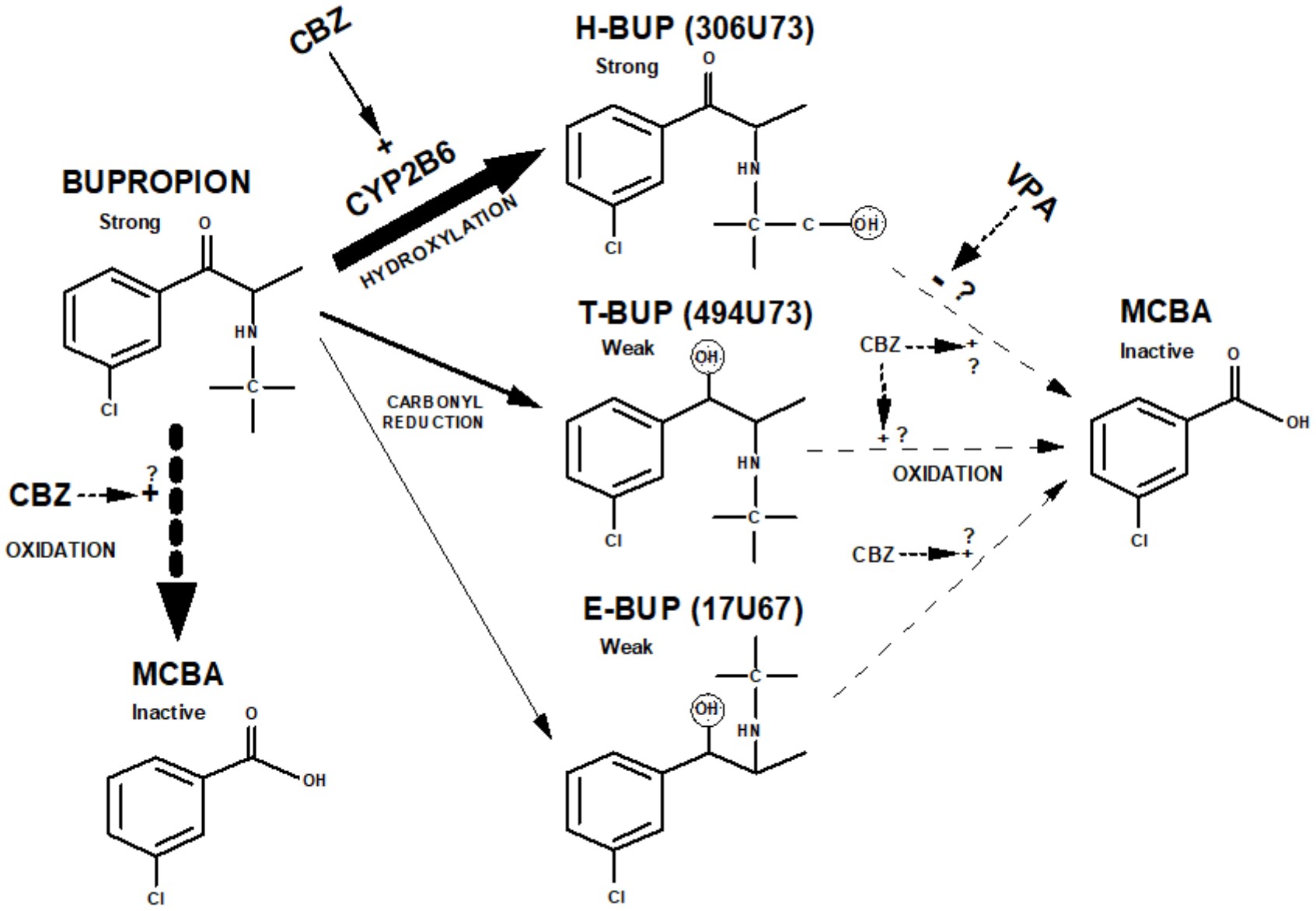
PHARMACOKINETICS OF SSRIs AND SNRIs

	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 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

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
high tyramine
cheese
chianti
fava
...

DRUGS
decongestants
opiates
SSRIs, SNRIs, CMI
stimulants
...
nefazodone ?
bupropion ?
(Li, VPA okay)
(CBZ okay?)

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
- CYP2D6 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 potential ↑ terfenadine, astemizole, cisapride
- 3A4 substrate; nonlinear kinetics
- Moderate therapeutic index (sedation)

NEFAZODONE INTERACTIONS

NEFAZODONE →↑ DRUG

VIA 3A3/4

alprazolam
triazolam
carbamazepine
cyclosporin
terfenadine ?
astemizole ?
cisapride ?

ANTIHISTAMINE INTERACTIONS

ANTIHISTAMINES

METABOLIZED VIA 3A3/4

terfenadine (Seldane)*
astemizole (Hismanal)*
loratadine (Claritin)
cetirizine (Zyrtec)
fexofenadine (Allegra)

*cardiotoxic

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

ANXIOLYTIC METABOLISM

CLASS / DRUG	SUBSTRATE OF	INHIBITED BY
2-KETO clorazepate diazepam flurazepam	2C19, 3A3/4	fluoxetine fluvoxamine
TRIAZOLO alprazolam triazolam	3A3/4	fluoxetine fluvoxamine nefazodone
7-NITRO clonazepam nitrazepam	N-reduction	-
3-HYDROXY lorazepam oxazepam temazepam	conjugation	-

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

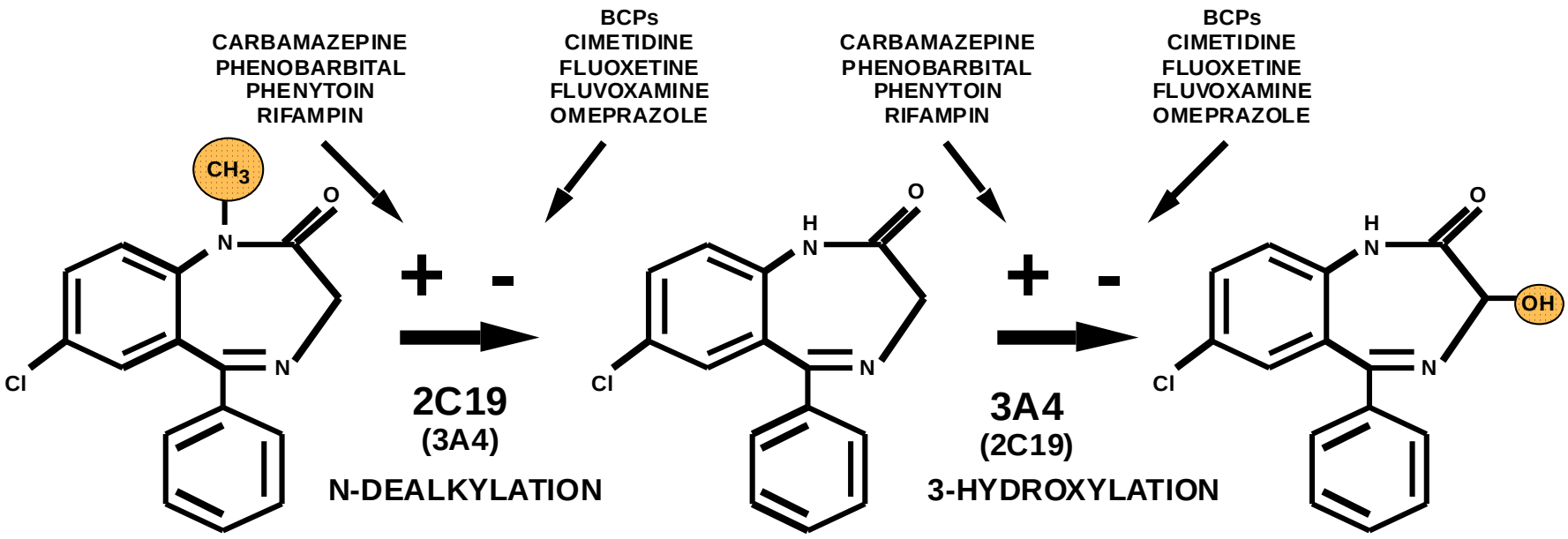
alprazolam
triazolam

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

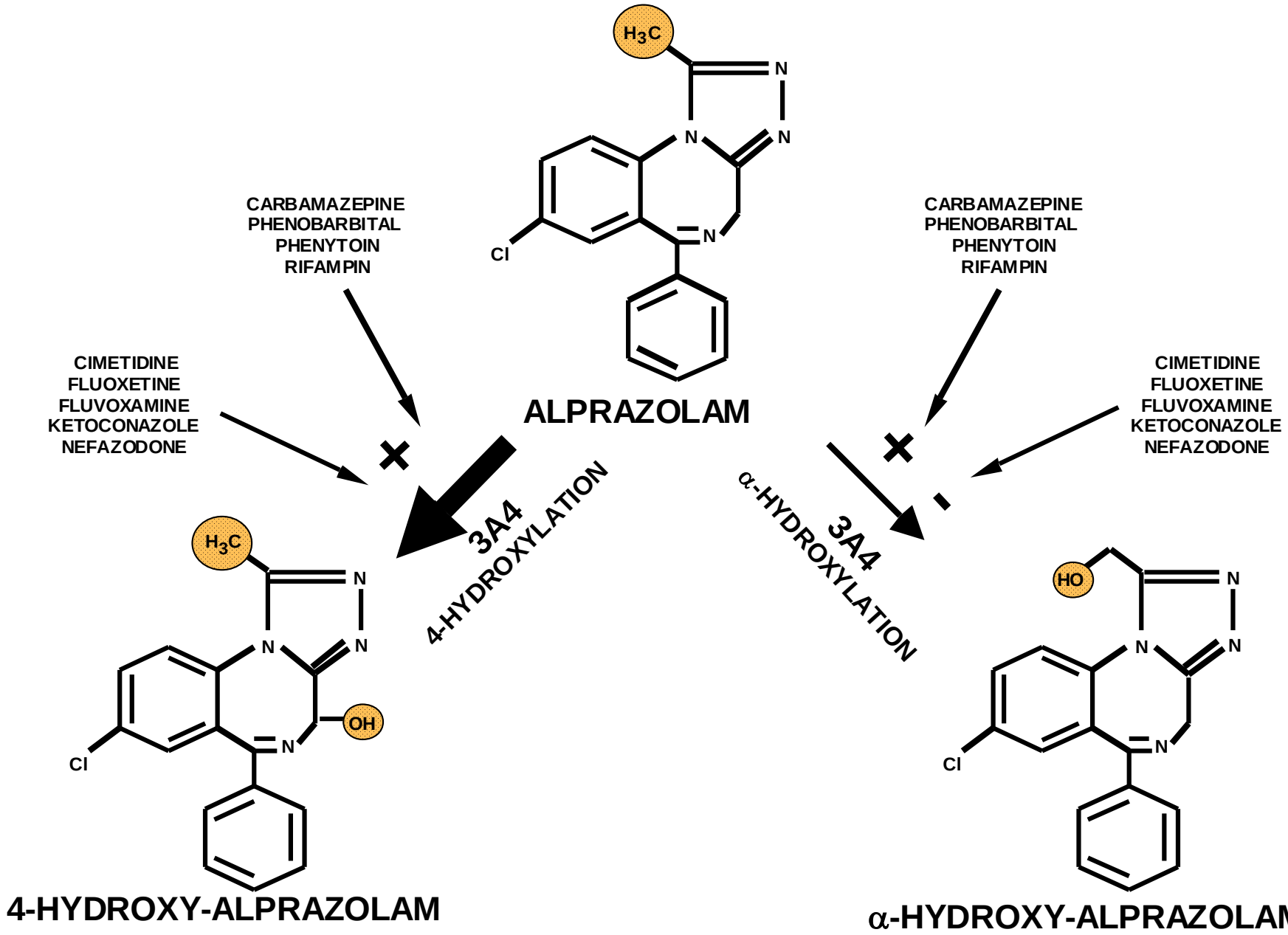
N-DESMETHYL-DIAZEPAM

ACTIVE
METABOLITE

OXAZEPAM

ACTIVE
3-HYDROXY-BZ
(DIRECTLY CONJUGATED)

ALPRAZOLAM METABOLISM



ANTIPSYCHOTIC METABOLISM

DRUG	SUBSTRATE OF	INHIBITS
haloperidol	2D6	2D6
fluphenazine	?	2D6
perphenazine	2D6	2D6
thioridazine	2D6	2D6
clozapine	1A2, ± 2D6	-
risperidone	2D6	-
olanzapine	1A2	-
sertindole	2D6, 3A3/4	-

ANTIPSYCHOTICS

- 100% absorbed (↓ with antacid); F = 20 - 80%
- 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)

ANTIPSYCHOTIC INTERACTIONS

DRUG→↑AP
tricyclics
fluoxetine
 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
- Low therapeutic index (sedation)

CLOZAPINE INTERACTIONS

DRUG →↑ CLOZ
fluoxetine
fluvoxamine
cimetidine
risperidone
± valproate

DRUG →↓ CLOZ
cigarettes
carbamazepine
phenytoin

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, $t_{1/2}$ = 21 h)
- CYP2D6 substrate
- Mod therapeutic index (neurotoxicity)

OLANZAPINE

- Well absorbed
- 93% bound; V = 15 L / kg
- $t_{1/2}$ = 30 h; Cl = 400 mL / min
- 5 - 20 mg / d
- Metabolites - 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 - 750 mg / d (in 2 or 3 divided doses)
- Inactive sulfoxide metabolite via CYP3A4
- PHT, thioridazine → ↓ quetiapine
- quetiapine →↑ warfarin
- Well tolerated with lithium
- No effect on lithium levels

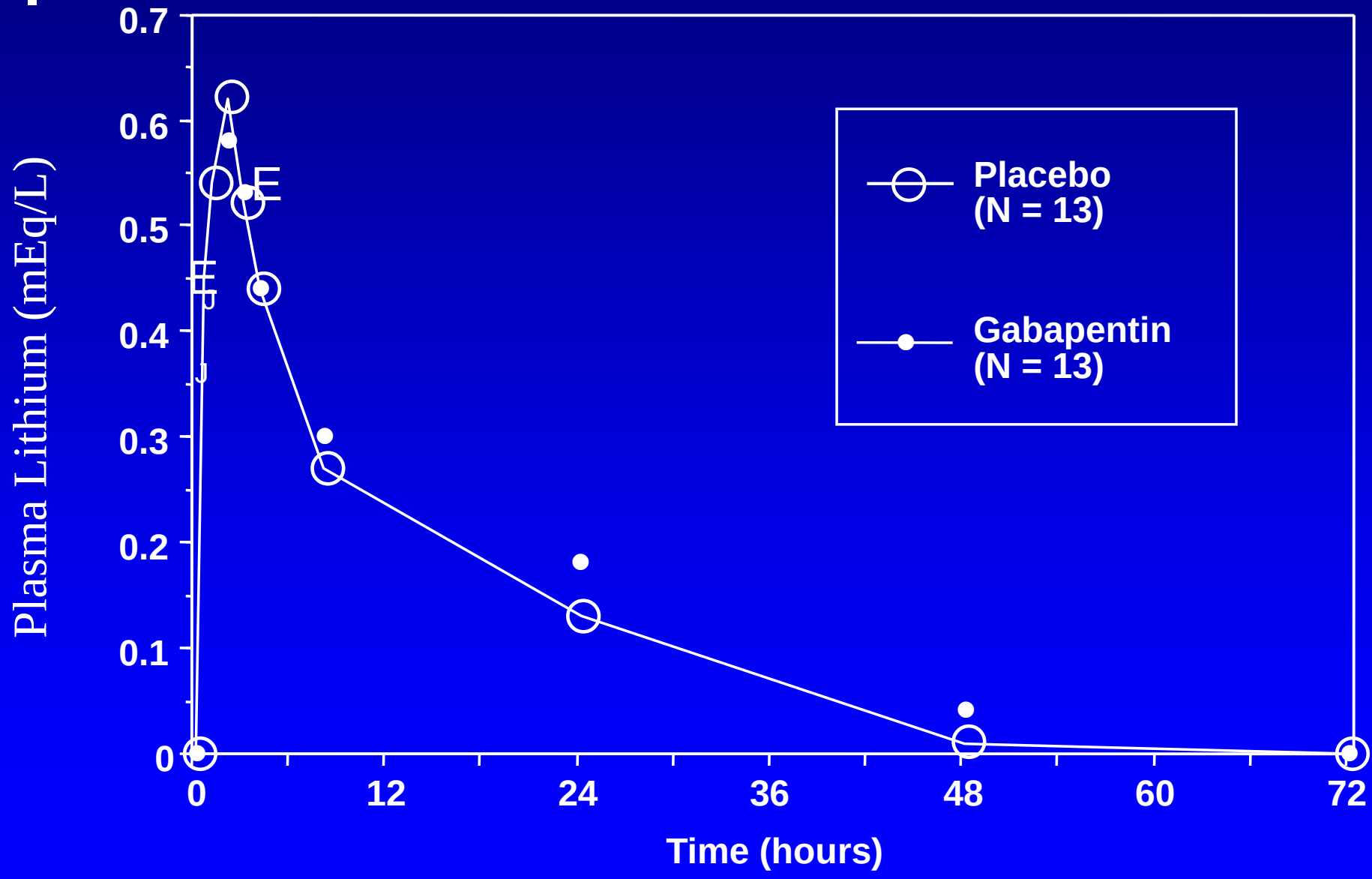
ANTICONVULSANT ELIMINATION

DRUG	SUBSTRATE OF	INDUCES / INHIBITS
carbamazepine	3A3/4	induces 3A4, ...
valproate	conj>□-oxid>P450oxid	weak inhibitor
felbamate	renal>conj,oxid	induces 3A4
gabapentin	renal excretion	-
lamotrigine	conjugation	-
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)**

GABAPENTIN DOES NOT ALTER LITHIUM KINETICS



Frye MA, et al. J Clin Psychopharmacol 1998 Dec;18(6):461-4.

LAMOTRIGINE

- F = 98%; 55% bound; V = 1 L / kg
- Rx t1/2 (h) Cl (mL/min) dose (mg/d)

Rx	t1/2 (h)	Cl (mL/min)	dose (mg/d)
monoRx	28	40	150 [25 - 250]
with CBZ	14	80	175 [25 - 350]
with VPA	56	20	75 [25 - 200]

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

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 mono Rx $t_{1/2}$ = 4 h with inducers
- Cl = 109 mL / min
- TGB is a CYP3A 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 $\rightarrow\downarrow$ VPA (10%)

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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- DeVane CL: Fundamentals of Monitoring Psychoactive Drug Therapy. Williams & Wilkins, Baltimore 1990.
- Evans WE, et al: Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring, 3rd ed. Applied Therapeutics, Vancouver, WA 1992.
- Ketter TA, et al: Metabolism and excretion of mood stabilizers and new anticonvulsants. Cell Mol Neurobiol 1999;19(4):511-32..

Post Lecture Exam
Question 1

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

A. Volume of distribution (V)
B. Half life (t1/2)
C. Clearance (C1)
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 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