

# **Pharmacokinetics of Psychotropic Drugs**

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# Teaching Points

- **Key pharmacokinetic parameters include volume of distribution, half life, and clearance.**
- **Most drugs undergo hepatic metabolism, and are thus at risk for drug interactions related to hepatic metabolism, but a few drugs (such as lithium) have renal excretion, and are thus at risk for drug interactions related to renal excretion.**
- **Characterizing medications as substrates, inducers, and inhibitors of specific cytochrome p450 metabolic enzymes can help predict and prevent adverse events related to drug interactions.**
- **The two most important cytochrome P450 isoforms mediating drug interactions in psychiatric patients receiving combination therapies are CYP2D6 and CYP3A3/4.**

# 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 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
- **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<sub>1/2</sub>**  
(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  $V \times [\text{desired conc. change}]$ )

**t<sub>1/2</sub>**  
(half life)  
( $t_{1/2} = .7 \times V / Cl$ )

**Time to steady state = 5 x t<sub>1/2</sub>**

**Cl**  
(clearance)

**Steady state concentration**  
( $C_{ss} = \text{dose} \times \text{dosing interval} \times F / Cl$ )

# 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<sub>1/2</sub>**

(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



- **Lipophilicity & binding**
- **Many drugs 80 - 95% protein bound**
  - Albumin - acids
  - $\alpha_1$ -acid glycoprotein - bases, neutral
  - Lipoproteins - bases, neutral
- **Binding profiles**
  - Alb: VPA, PHT, diazepam
  - Alb +  $\alpha_1$ AG: CBZ, verapamil
  - Alb +  $\alpha_1$ AG + 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-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 monohydroxyderivative (MHD)
valproate	2-ene-valproate, 4-ene-valproate <u>(toxic)</u>
amitriptyline	nortriptyline, hydroxynortriptyline
IMI/DMI	imipramine desipramine, hydroxy- IMI and DMI
amoxapine	hydroxyamoxapine fluoxetine norfluoxetine sertraline N-desmethylsertraline ( $\pm$ ) citalopram di/desmethylcitalopram
venlafaxine	O-desmethylvenlafaxine bupropion hydroxybupropion
trazodone	m-chlorophenylpiperazine <u>(m-CPP)</u>
nefazodone	m-CPP hydroxynefazodone



# ACTIVE METABOLITES

diazepam

desmethyldiazepam  
desmethyldiazepam  
hydroxyalprazolam

chlorpromazine

haloperidol  
loxapine  
clozapine

hydroxyrisperidone

N-desmethyldiazepam

clorazepate N-  
chlordiazepoxide N-  
alprazolam apha-  
flurazepam  
desalkylflurazepam  
buspirone  
pyrimidinylpiperazine (1-PP)

hydroxychlorpromazine

thioridazine mesoridazine  
reduced haloperidol  
amoxapine  
desmethyclozapine ( $\pm$ )

risperidone 9-  
aripiprazole dehydro-

# PHARMACODYNAMIC CONCEPTS

<u>CONCEPT</u>	<u>DEFINITION / RELEVANCE</u>
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
- 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

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

# CYP2D6

## SUBSTRATES

atomoxetine  
duloxetine  
 ± fluoxetine  
 ± mirtazapine  
 paroxetine  
 venlafaxine  
 2° & 3° tricyclics  
 (hydroxylation)  
 trazodone  
  
 ± clozapine  
 haloperidol  
 fluphenazine  
 perphenazine  
 risperidone  
 thioridazine  
  
 codeine  
 mexiletine  
**IC antiarrhythmics**  
 β blockers

## INHIBITORS

bupropion  
 fluoxetine  
 ± fluvoxamine  
 paroxetine  
 ± sertraline  
 moclobemide

fluphenazine  
 haloperidol  
 perphenazine  
 thioridazine

amiodarone  
 cimetidine  
 methadone  
 quinidine  
 Ritonavir et al

## INDUCERS

-



# CYP3A4,5,7

## SUBSTRATES

± citalopram  
 ± mirtazapine  
 nefazodone  
 reboxetine  
 sertraline  
 3° tricyclics  
 (demethylation)  
 alprazolam  
 diazepam  
 midazolam  
 triazolam  
 buspirone  
 CBZ

Ca blockers  
 H1 blockers  
 local anesthetics  
 macrolides  
 quinidine  
 steroids

## INHIBITORS

fluvoxamine  
 nefazodone  
 diltiazem  
 verapamil

cimetidine  
 imidazoles  
 macrolides  
 naringenin

## INDUCERS

CBZ  
 phenobarbital  
 phenytoin

dexamethasone  
 rifampin

# 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



# 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
<u>Prebubes</u>	(=)	(↑)	(↑)
Elderly	(=)	(= ↓)	↓
Pregnant	(= ↓)	(= ↓ ↑)	↑
Manic	(=)	(=)	(↑)
Renal d.	↓	↓	↓
Liver d.	(= ↓)	↓	(= ↓)

# MOOD STABILIZER AND ANTICONVULSANT METABOLISM

<u>DRUG</u>	<u>SUBSTRATE OF</u>	<u>INDUCES / INHIBITS</u>
lithium carbamazepine valproate	renal excretion <u>3A4, 3A5-7</u> conjugation $\beta$ -hydroxylation P450 oxidation	- induces 3A4,5,7 ... weak inhibitor
phenytoin barbiturates lamotrigine gabapentin	2C9/10, $\pm$ 2C19 2C19 <u>UGT1A4?</u> renal excretion	induces 3A4,5,7, ... induce 3A4,5,7, ... <u>mildly self</u> -

# LITHIUM

- 100% absorbed;  $F = 100\%$
- 0% bound;  $V = 1 \text{ L / kg}$
- $t_{1/2} = 24 \text{ h}$ ;  $Cl = 10 - 40 \text{ mL / min}$
- $Cl = .25 \times \text{creatinine Cl}$
- 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



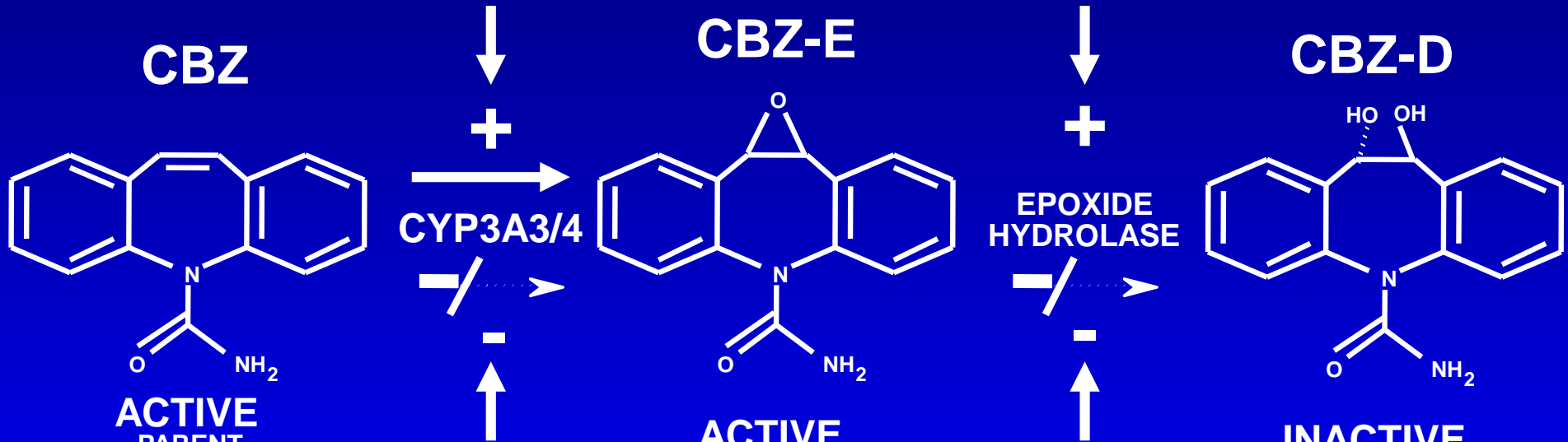
# CARBAMAZEPINE

- Erratic absorption;  $F = 80\%$
- 75% bound;  $V = 1 \text{ L / kg}$
- $t_{1/2} = 24 \text{ h}$ ;  $Cl = 25 \text{ mL / min}$  (pre-induction)  
 $t_{1/2} = 8 \text{ h}$ ;  $Cl = 75 \text{ mL / min}$  (post-induction)
- 400 - 1600 mg / d; 4 - 12 mcg / mL
- Active CBZ-10,11-epoxide metabolite ( $t_{1/2}$  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**

**ACTIVE  
 EPOXIDE  
 METABOLITE**

**INACTIVE  
 DIOL  
 METABOLITE**

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

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

\* molecular biochemical evidence supports CYP3A4/4

# Carbamazepine

## Decreases Levels of Other Drugs

### (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

Bepidil  
Dihydropyridine CCBs  
Oxiracetam (?)  
Paclitaxel  
Quinidine  
Remacemide (?)  
Repaglinide  
Theophylline (?)  
Thoralaralyroid  
hormones

# 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)

# CYP3A4-MEDIATED CBZ DRUG INTERACTIONS

CBZ →↓ DRUG

3° tricyclics  
(demethylation)

Ca blockers  
CBZ  
benzodiazepines

dexamethasone  
oral contraceptives  
prednisolone  
local anesthetics  
ethosuximide

DRUG →↑ CBZ

Fluoxetine  
fluvoxamine  
Nefazodone

Ca blockers

danazol

cimetidine

clarithromycin  
erythromycin

DRUG →↓ CBZ

CBZ  
phenobarbital  
phenytoin (?)

# VALPROATE

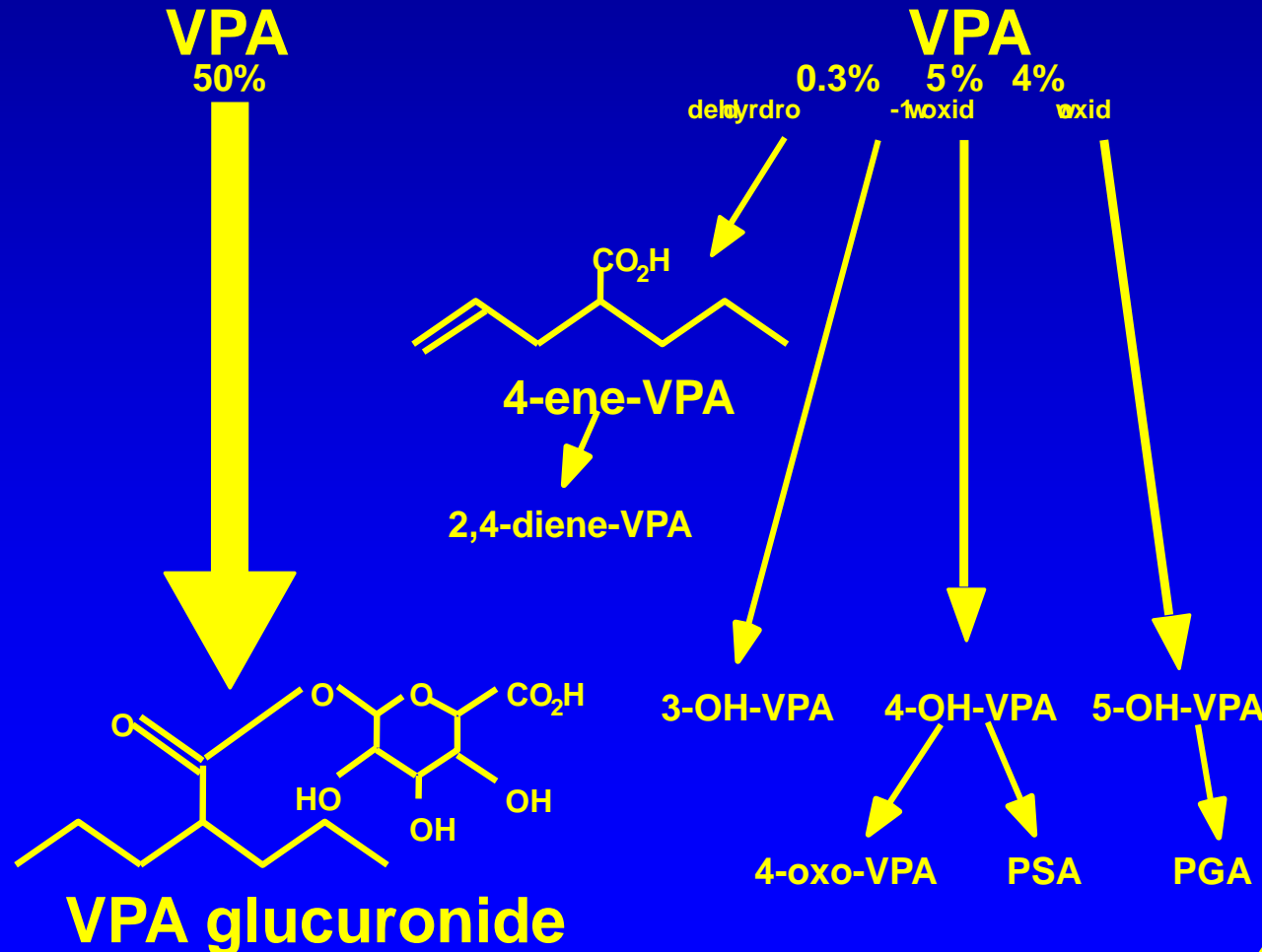
- 100% absorbed;  $F = 100\%$
- 80 - 90% bound (saturable);  $V = 0.1 - 0.2 \text{ L / kg}$
- $t_{1/2} = 12 \text{ h}$ ;  $Cl = 10 \text{ mL / min}$
- 750 - 4000 mg / d; 50 - 125 mcg / mL
- Binding saturation-lower % bound at hi levels
- “Sublinear” kinetics, binding interactions
- 3 elimination routes
  - metabolites
  - 50% conjugation
    - glucuronides
  - 40%  $\beta$  oxidation
    - 2-ene-valproate, ...
  - 10% P450 oxidation
    - 4-ene-valproate, ...
- Some metabolic interactions
- Low-mod therapeutic index (g.i., neurotoxicity)

# VALPROATE METABOLISM

## Smooth Endoplasmic Reticulum

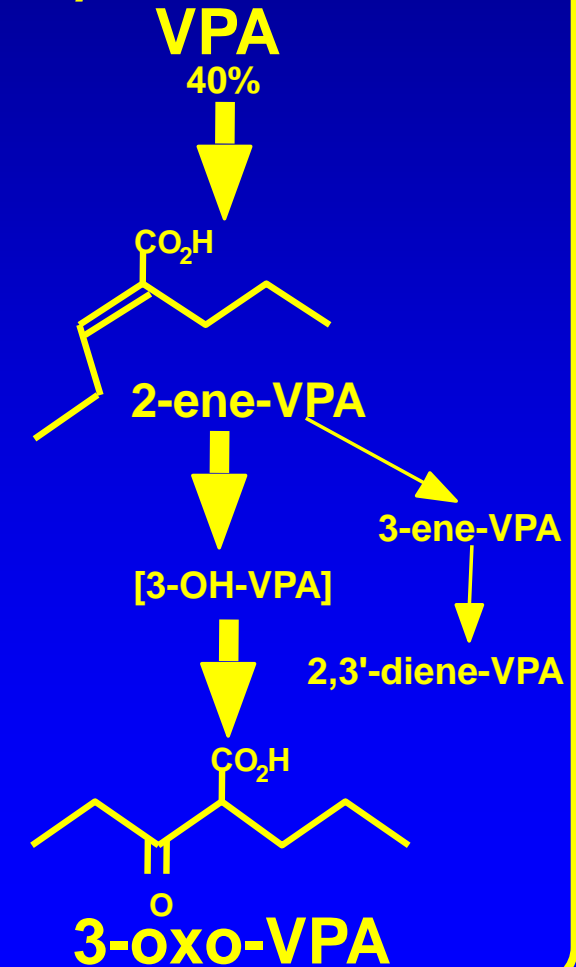
### CONJUGATION

### P450 OXIDATION



## Mitochondria

### $\beta$ OXIDATION



# VPA/PLASMA PROTEIN BINDING INTERACTIONS

VPA → ↑ FREE DRUG

CBZ  
diazepam  
phenytoin  
tiagabine  
tolbutamide  
warfarin

DRUG → ↑ FREE VPA

ASA  
NSAIDs



# DVPX METABOLIC INTERACTIONS

VPA →↑ DRUG

amitriptyline  
 CBZ-E  
 diazepam  
 ethosuximide  
 lamotrigine  
 lorazepam  
 nortriptyline  
 phenobarbital  
 phenytoin  
 zidovudine

DRUG →↑ VPA

ASA  
 cimetidine  
 fluoxetine  
 felbamate  
 erythromycin  
 phenothiazines

DRUG →↓ VPA

CBZ  
 ± lamotrigine  
 mefloquine  
 phenobarbital  
 phenytoin  
 rifampin

# KEY ISOFORMS FOR ANTIDEPRESSANT METABOLISM

<u>ISOFORM</u>	<u>SUBSTRATES</u>	<u>INHIBITORS</u>	<u>INDUCERS</u>
CYP1A2	TCAs, ± mirtaz, dulox	fluvoxamine	cigs, omep
CYP2C19	± citalopram, TCAs	fluox, fluvox	rifampin
CYP2D6	± fluoxetine ± mirtazapine paroxetine <u>dulox/venlafaxine</u> 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;  $V = 10 - 30 \text{ L / kg}$
- $t_{1/2} = 24 \text{ h}$ ;  $Cl = 300 - 1700 \text{ mL / min}$
- 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

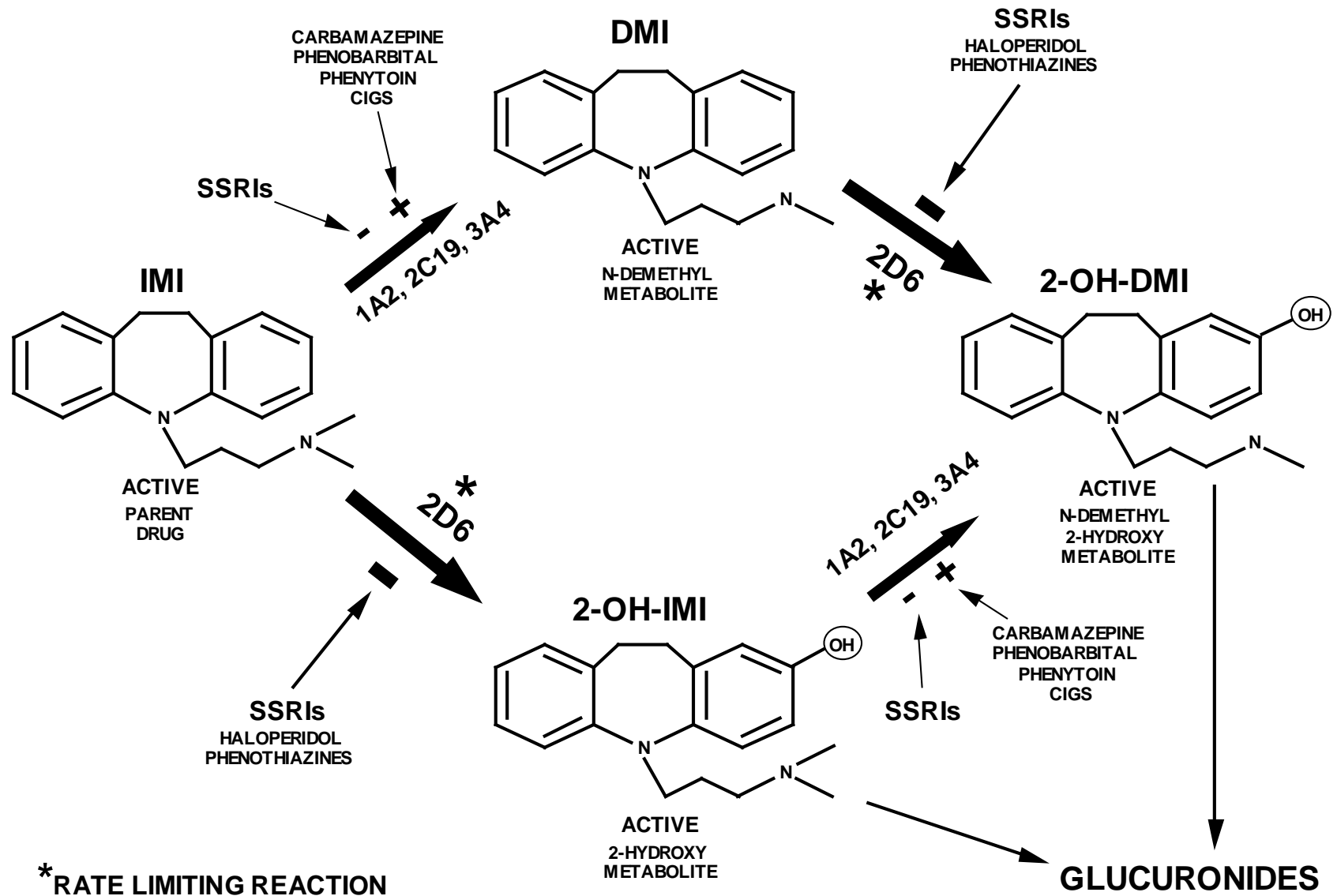
DRUG → ↓ TCA

carbamazepine  
chronic ethanol  
cigarette smoke  
phenobarbital  
phenytoin  
rifampin (?)

TCA → ↑ DRUG

phenytoin (?)  
warfarin (?)

# IMIPRAMINE METABOLISM



# 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

Duloxetine- substrate of CYP1A2 and CYP2D6 and modest inhibitor CYP2D6

# FLUOXETINE

- Well absorbed;  $F > 60\%$
- 95% bound;  $V = 20 - 45 \text{ L / kg}$
- $t_{1/2} = 4 \text{ d}$ ;  $Cl = 300 \text{ mL/ min}$
- 20 - 80 mg / d
- Norfluoxetine metabolite  
(active,  $t_{1/2} = \underline{7-14 \text{ d}}$ )
- 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;  $V = 17 \text{ L / kg}$
- $t_{1/2} = 21 \text{ h}$ ; 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;  $V = 20 \text{ L / kg}$
- $t_{1/2} = 16 \text{ h}$ ;  $Cl = 1600 \text{ mL/ min}$
- 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 3A4,5,7

alprazolam  
 diazepam  
 carbamazepine

VIA 2C9/10

phenytoin  
 warfarin

VIA 2D6

haloperidol

# SERTRALINE

- Absorption ↑ with food
- 98% bound;  $V = 20 \text{ L / kg}$
- $t_{1/2} = 26 \text{ h}$ ; 50 - 200 mg / d
- Desmethylsertraline metabolite  
(± active,  $t_{1/2} = 3 \text{ d}$ )
- 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

# VENLAFAXINE

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



# **CITALOPRAM-racemic mixture escitalopram-enantiomer**

- **Rapidly absorbed; F = 80%**
- **Absorption not affected by food**
- **80% bound; V = 12 L / kg**
- **$t_{1/2} = 35$  h; CI = 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

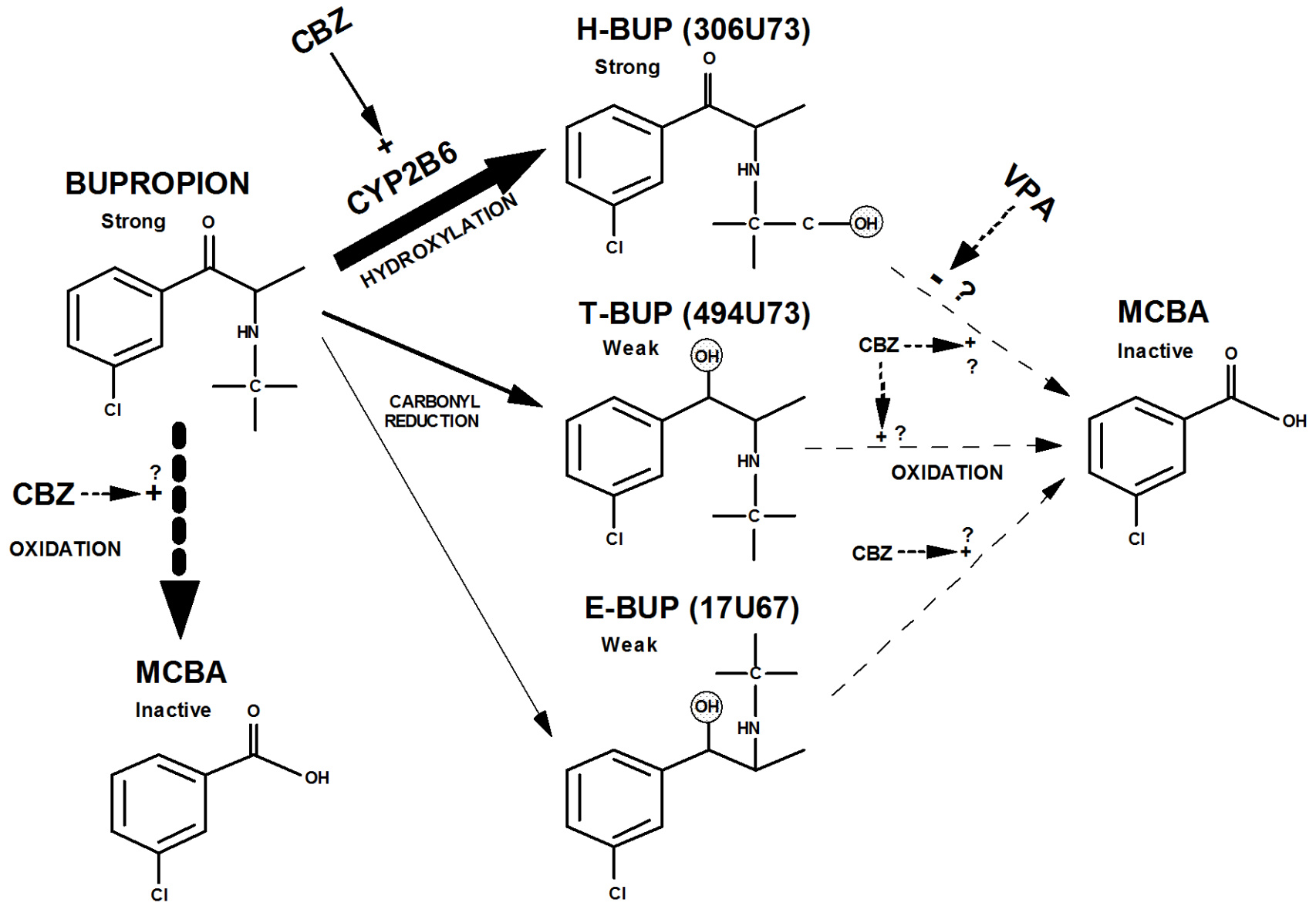
# PHARMACOKINETICS OF SSRIs AND SNRIs

	fluoxetine	sertraline	paroxetine	fluvoxamine	venlafaxine	citalopram
drug t <sub>1/2</sub>	4 d	26 h	21 h	16 h	5 h	35 h
metab t <sub>1/2</sub>	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;  $V = 20 \text{ L / kg}$
- $t_{1/2} = 20 \text{ h}$ ;  $Cl = 2300 \text{ mL / min}$
- 150 - 400 mg / d;  $> 10 \text{ ng / mL}$  (?)
- Extensive, CBZ-inducible metabolism
- Hydroxy-BUP (morpholinol) via CYP2B6
  - Threohydro-BUP via carbonyl reductase
  - Erythrohydro-BUP via carbonyl reductase
- 3 main active metabolites:  $t_{1/2}$  AUC<sub>ss</sub> 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



# 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

# MAO INHIBITORS

- **$t_{1/2}$  brief & not directly related to effects (irreversible MAO inhibition)**
- **Dose**
  - Phenzelzine - 45 - 90 mg
  - Tranylcypramine - 30 - 100 mg / d
- **85% MAO inhibition needed**
- **Therapeutic index**
  - Phenzelzine - low
  - Tranylcypramine - 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;  $V = 1 \text{ L / kg}$
- $t_{1/2} = 4 \text{ h}$ ;  $Cl = 120 - 200 \text{ mL / min}$
- 150 - 600 mg / d; 500 - 1500 ng / mL
- Active m-CPP metabolite  
(anxiogenic 5HT-1 agonist,  $t_{1/2} = 6 \text{ h}$ )
- May give with MAOIs
- CYP3A4 substrate
- Few metabolic interactions
- Low therapeutic index (sedation)

# NEFAZODONE

- 100% absorbed ( $\downarrow$  with food);  $F = 20\%$
- 99% bound;  $V = 0.5 \text{ L / kg}$
- $t_{1/2} = 3 \text{ h}$ ;  $Cl = 500 - 2000 \text{ mL / min}$
- 300 - 600 mg / d
- Active m-CPP metabolite  
(anxiogenic 5HT-1 agonist,  $t_{1/2} = 6 \text{ h}$ )
- Active hydroxy-nefazodone metabolite  
(blocks 5HT reuptake, 5HT-2,  $t_{1/2} = 3 \text{ h}$ )
- 3A4 inhibitor:  $\uparrow$  triazolam, alprazolam, carbamazepine
- 3A4 substrate; nonlinear kinetics
- Moderate therapeutic index (sedation, hepatotoxicity)

# NEFAZODONE INTERACTIONS

NEFAZODONE →↑ DRUG

VIA 3A3/4

alprazolam

triazolam

carbamazepine

cyclosporin

# ANTI-HISTAMINE INTERACTIONS

## ANTI-HISTAMINES

### METABOLIZED VIA 3A3/4

loratadine (Claritin)  
cetirizine (Zyrtec)  
fexofenadine (Allegra)

## DRUG → ↑ ANTI-HISTAMINE

### VIA 3A3/4

ketoconazole  
itraconazole  
fluconazole  
erythromycin  
clarithromycin  
troleandomycin  
nefazodone ?  
flvoxamine ?

# MIRTAZAPINE

- **F = 50%; 85% bound; V = 4 L / kg**
- **t<sub>1/2</sub> = 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**

# ANXIOLYTIC METABOLISM

\*

<u>CLASS / DRUG</u>	<u>SUBSTRATE OF</u>	<u>INHIBITED BY</u>
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 <u>UGTs</u>	-

# BENZODIAZEPINES

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



# BENZODIAZEPINES

<u>2-KETO</u>	<u>TRIAZOLO</u>	<u>7-NITRO</u>	<u>3-HYDROX</u>
clorazepate diazepam flurazepam	alprazolam triazolam	clonazepam nitrazepam	lorazepam oxazepam temazepam
N-dealk [2C19] - 3-hydrox [3A4]	4-hydrox [3A4], $\alpha$ -hydrox [3A4]	N-reduction	direct conjugation
active, long t <sub>1/2</sub> metabs	active, short t <sub>1/2</sub> 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

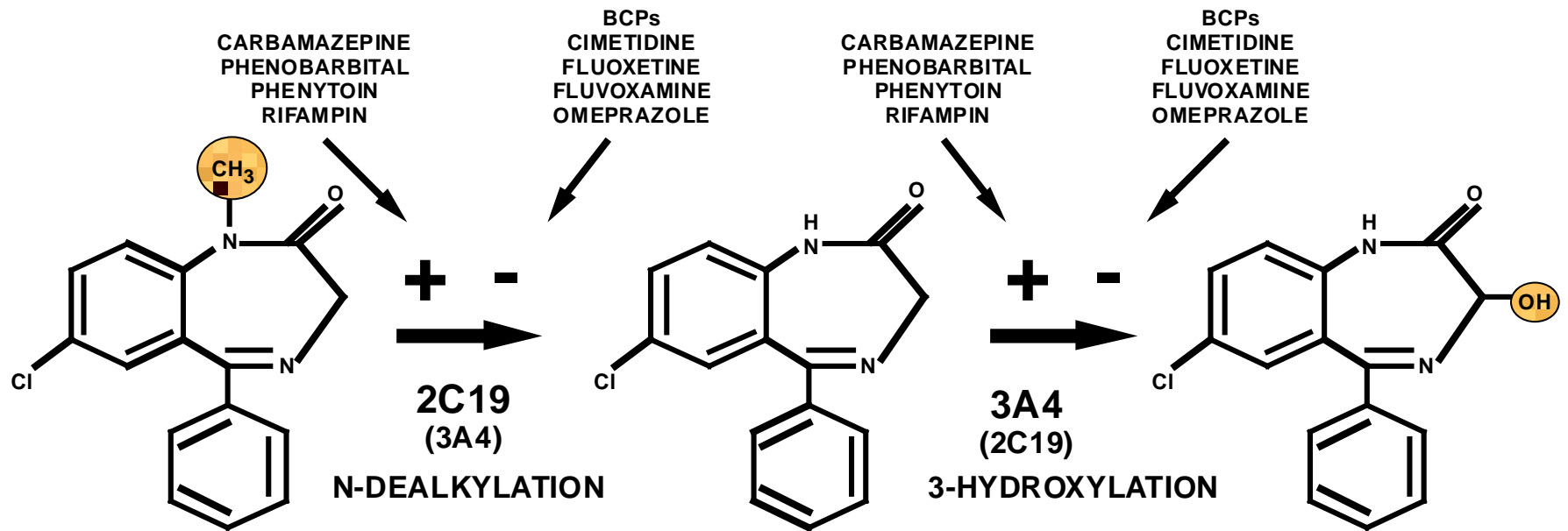
alprazolam  
triazolam

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

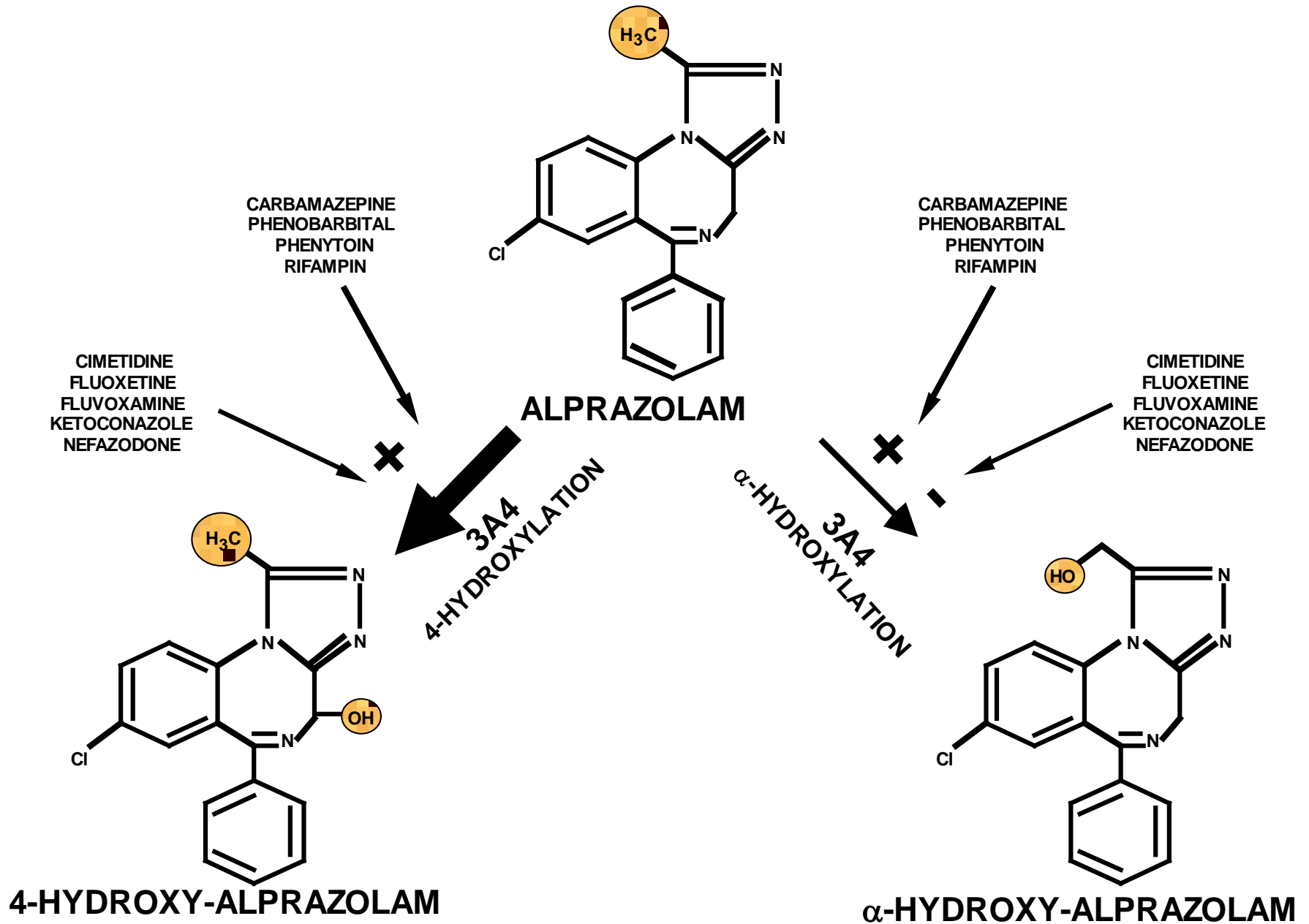
**N-DESMETHYL-DIAZEPAM**

ACTIVE  
METABOLITE

**OXAZEPAM**

ACTIVE  
3-HYDROXY-BZ  
(DIRECTLY CONJUGATED)

# ALPRAZOLAM METABOLISM



# ANTIPSYCHOTIC METABOLISM

<u>DRUG</u>	<u>SUBSTRATE OF</u>	<u>INHIBITS</u>
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;  $V = 10 - 40 \text{ L / kg}$
- $t_{1/2} = 12 - 24 \text{ h}$ ;  $Cl = 70 - 600 \text{ mL / min}$
- 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;  $V = 5 \text{ L / kg}$**
- **$t_{1/2} = 12 \text{ h}$ ;  $Cl = 750 \text{ mL / min}$**
- **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

fluoxetine

fluvoxamine

cimetidine

risperidone

± valproate

## DRUG → ↓ CLOZ

Cigarette smoke

carbamazepine

phenytoin

# RISPERIDONE

- 90 - 100% absorbed;  $F = 70\%$
- 90% bound;  $V = 1 \text{ L / kg}$
- $t_{1/2} = 3 \text{ h}$ ;  $Cl = 400 \text{ mL / min}$
- 4 - 16 mg / d
- 9-hydroxy-risperidone metabolite(active,  $t_{1/2} = 21 \text{ h}$ ) is substrate CYP3A4
- Risperidone is CYP2D6 substrate
- Carbamazepine  $\rightarrow$   $\downarrow$  risperidone
- Fluoxetine  $\rightarrow$   $\uparrow$  risperidone
- Mod therapeutic index (neurotoxicity)

# OLANZAPINE

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

# QUETIAPINE

- 100% absorbed;  $F = 100\%$
- 83% bound;  $V = 10 \text{ L / kg}$
- $t_{1/2} = 6 \text{ h}$ ;  $\text{Cl} \downarrow 40\%$  in elderly
- 50 - 800 mg / d (in divided doses)
- Inactive sulfoxide metabolite via CYP3A4
- PHT, thioridazine  $\rightarrow \downarrow$  quetiapine
- Quetiapine  $\rightarrow \uparrow$  warfarin
- Well tolerated with lithium
- No effect on lithium levels

# ZIPRASIDONE

- 60% absorbed with food (30% unfed)
- 99% bound;  $V = 1.5 \text{ L / kg}$
- $t_{1/2} = 6.6 \text{ h}$ ;  $Cl = 525 \text{ mL / min}$
- 40 - 160 mg / d p.o.; 20 - 40 mg / d i.m.  
(in 2 divided doses)
- Metabolism
  - 2/3 aldehyde oxidase reduction
  - 1/3 P450 oxidation (CYP3A4)
- carbamazepine  $\rightarrow$   $\downarrow$  ziprasidone
- ketoconazole  $\rightarrow$   $\uparrow$  ziprasidone
- No effect on lithium or BCP levels

# ARIPIPRAZOLE

- $F = 87\%$
- 99% bound;  $V = 4.9 \text{ L / kg}$
- $t_{1/2} = 75 \text{ h}$
- 10 - 30 mg / d
- Metabolized by CYP2D6, CYP3A4
- Active dehydro-aripiprazole metabolite ( $t_{1/2} = 94 \text{ h}$ )
- carbamazepine  $\rightarrow$   $\downarrow$  aripiprazole
- ketoconazole  $\rightarrow$   $\uparrow$  aripiprazole
- quinidine  $\rightarrow$   $\uparrow$  aripiprazole
- Not affected by lithium or VPA

# ANTICONVULSANT ELIMINATION

<u>DRUG</u>	<u>SUBSTRATE OF</u>	<u>INDUCES / INHIBITS</u>
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<sub>1/2</sub> = 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)**

# LAMOTRIGINE

- F = 98%; 55% bound; V = 1 L / kg

Rx	t <sub>1/2</sub> (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 → ↑ CBZ neurotoxicity (dynamic vs ↑ CBZ-E)
- LTG → ± ↓ VPA
- VPA, ± sertaline → ↑ LTG
- CBZ, PHT, PB, PRIM, BCPs → ↓ LTG

# Lamotrigine Titration Influenced by Valproate and Carbamazepine

\*

Lamotrigine Titration in Adults <sup>1,2</sup>	
Week	Daily Dose
1	25 mg
2	25 mg
3	50 mg
4	50 mg
Week 5 onward	Add 50-100 mg/wk as clinically indicated
Maintenance	100-400 mg

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

<sup>1</sup> Guberman et al. Epilepsia. 1999; <sup>2</sup> Physicians' Desk Reference. 2006.

# TOPIRAMATE

- $F = 80\%$ ; 15% bound;  $V = 0.8 \text{ L / kg}$
- $t_{1/2} = 24 \text{ h}$ ;  $Cl = 25 \text{ mL / min}$
- 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  $V = 0.7 \text{ L / kg}$
- OXC  $t_{1/2} = 2 \text{ h}$ ; MHD  $t_{1/2} = 9 \text{ h}$ ;
- 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  $\rightarrow$   $\downarrow$  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-sulfamoylacetophenol (SMAP)
- 100 mg/d  $\rightarrow$   $\uparrow$  100 mg/d q 2wks -up to 300-600 mg/d
- CBZ, PHT, PB  $\rightarrow$   $\downarrow$  ZNS; LTG  $\rightarrow$   $\uparrow$  ZNS

# LEVETIRACETAM

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



# Ca CHANNEL BLOCKERS

\*

- 90 - 100% absorbed;  $F = 10 - 50\%$
- 80 - 90% bound;  $V = 1 - 5 \text{ L / kg}$
- $t_{1/2} = 1 - 6 \text{ h}$ ;  $Cl = 70 - 140 \text{ mL / min}$
- 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 ( $t_{1/2} = 10 \text{ h}$ )
- 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**

# REFERENCES

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- **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 ( $t_{1/2}$ )
  - 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 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