Pharmacokinetics of Psychototropic 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.
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
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

<table>
<thead>
<tr>
<th>CONCEPT</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (vol of distrib)</td>
<td>Volume needed to contain drug at concentration same as plasma</td>
</tr>
<tr>
<td>$t_{1/2}$ (half life)</td>
<td>Time for [drug] to ↓ 50%</td>
</tr>
<tr>
<td>Cl (clearance)</td>
<td>Volume of blood cleared of drug per unit time</td>
</tr>
</tbody>
</table>
## PHARMACOKINETIC CONCEPTS

<table>
<thead>
<tr>
<th>CONCEPT</th>
<th>RELEVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V</strong> (vol of distrib)</td>
<td>Extracirculatory distribution (binding, lipophilicity)</td>
</tr>
<tr>
<td></td>
<td>Loading dose (Load with V x [desired conc. change])</td>
</tr>
<tr>
<td>t_{1/2}</td>
<td>Time to steady state = 5 × t_{1/2}</td>
</tr>
<tr>
<td>(half life)</td>
<td></td>
</tr>
<tr>
<td>(t_{1/2} = 0.7 × V / Cl)</td>
<td></td>
</tr>
<tr>
<td>Cl (clearance)</td>
<td>Steady state concentration (C_{ss} = dose × dosing interval × F / Cl)</td>
</tr>
</tbody>
</table>
## PHARMACOKINETIC CONCEPTS

<table>
<thead>
<tr>
<th>CONCEPT</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V )</td>
<td>( \text{Li} - 1 \text{ L / kg; TCAs} - 10 \text{ L / kg} )</td>
</tr>
<tr>
<td></td>
<td>(vol of dist) (dialysis effective; dialysis ineffective)</td>
</tr>
<tr>
<td></td>
<td>( \text{VPA} - 0.2 \text{ L / kg} )</td>
</tr>
<tr>
<td></td>
<td>(Load with 0.2 L/kg x 100 mg/L = 20 mg/kg)</td>
</tr>
<tr>
<td>( t_{1/2} )</td>
<td>( \text{fluoxetine} - 5 \text{ wk MAOI wait} )</td>
</tr>
<tr>
<td></td>
<td>( \text{venlafaxine} - 2 \text{ wk MAOI wait} )</td>
</tr>
<tr>
<td>( \text{Cl} )</td>
<td>↑ [Li] in renal failure</td>
</tr>
<tr>
<td></td>
<td>↑ [diazepam] in liver failure</td>
</tr>
</tbody>
</table>
**ABSORPTION**

- Bioavailability = % reaching circulation as compared to IV \((F = \text{absorption} - \text{first pass metabolism})\)

- **Affected by food**
  \((\uparrow\text{ sertraline, ziprasidone}; \downarrow\text{ nefazodone absorption})\)

- **Affected by enteric/hepatic metabolism**
  \((\text{tyramine - MAO; terfenadine - CYP3A4})\)

- **Speed affected by enteric motility**
  \((\uparrow\text{ with metoclopramide}, \downarrow\text{ with TCAs})\)

- **Speed affected by formulation**
  \((\text{solution} > \text{suspension} > \text{capsule} > \text{tab} > \text{enteric coated tab})\)
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, monohydroxyderivitive (MHD), 2-ene-valproate, 4-ene-valproate (toxic)
- Valproate: nortriptyline, hydroxynortiptyline
- Amitriptyline: imipramine, desipramine, hydroxy-IMI and DMI
- IMI/DMI: hydroxyamoxapapine, fluoxetine, norfluoxetine, sertraline, N-desmethylsetraline (±), citalopram, di/desmethylcitalopram
- Amoxapine: O-desmethylvenlafaxine, bupropion, hydroxybupropion
- Venlafaxine: m-chlorophenylpiperazaine (m-CPP), m CPP, hydroxyvenlafaxine, nefazodone
<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>diazepam</td>
<td>N-desmethyldiazepam</td>
</tr>
<tr>
<td>desmethyldiazepam</td>
<td>clorazepate</td>
</tr>
<tr>
<td>desmethyldiazepam</td>
<td>N-chlordiazepoxide</td>
</tr>
<tr>
<td>hydroxyalprazolam</td>
<td>alprazolam</td>
</tr>
<tr>
<td></td>
<td>apha-hydroxyalprazolam</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>hydroxychlorpromazine</td>
</tr>
<tr>
<td>haloperidol</td>
<td>thioridazine</td>
</tr>
<tr>
<td>loxapine</td>
<td>mesoridazine</td>
</tr>
<tr>
<td>clozapine</td>
<td>reduced haloperidol</td>
</tr>
<tr>
<td></td>
<td>amoxapine</td>
</tr>
<tr>
<td>hydroxyrisperidone</td>
<td>desmethyclozapine (±)</td>
</tr>
<tr>
<td></td>
<td>risperidone</td>
</tr>
<tr>
<td></td>
<td>aripiprazole dehydo-</td>
</tr>
</tbody>
</table>
# PHARMACODYNAMIC CONCEPTS

<table>
<thead>
<tr>
<th>CONCEPT</th>
<th>DEFINITION / RELEVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic index</td>
<td>Efficacy relative to toxicity</td>
</tr>
<tr>
<td>Dose-response curve</td>
<td>Linear, sigmoidoidal, curvilinear relationships</td>
</tr>
<tr>
<td>Tolerance</td>
<td>↓ therapeutic or adverse responses with time</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>Discontinuation effects</td>
</tr>
<tr>
<td>Response latency</td>
<td>Delay to onset of effects</td>
</tr>
</tbody>
</table>
## PHARMACODYNAMIC CONCEPTS

<table>
<thead>
<tr>
<th>CONCEPT</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic index</td>
<td>High for SSRIs, low for Li</td>
</tr>
<tr>
<td>Dose-response curve</td>
<td>Curvilinear for nortriptyline (therapeutic window)</td>
</tr>
<tr>
<td>Tolerance</td>
<td>BZ (sedation, anticonvulsant opiates (analgesia)</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>BZ (insomnia, anxiety)</td>
</tr>
<tr>
<td>Response latency</td>
<td>BZ - minutes Li, CBZ, VPA - days to wks</td>
</tr>
</tbody>
</table>
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
D - subfamily
6 - gene

(> 40% homology)
(> 55% homology)
### Key Isoforms for Drug Metabolism

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>TCAs, cloz, olanz</td>
<td>cipro, fluvoxamine</td>
<td>Cig smoke, omeprazole</td>
</tr>
<tr>
<td>CYP2C9/10</td>
<td>phenytoin, THC S-warfarin</td>
<td>fluvoxamine</td>
<td>rifam, barb</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>BZs, TCAs</td>
<td>fluox, fluvox</td>
<td>rifampin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>TCAs, parox, mirtaz, venla, ±fluox</td>
<td>parox, fluox ±fluvox ±sertra disulfiram</td>
<td>-</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Etoh</td>
<td>fluoxetine</td>
<td>Etoh, INH</td>
</tr>
<tr>
<td>CYP3A4,5,7</td>
<td>BZs, CBZ Sertraline, Nefazodone, TCAs, mirtaz, Ca blockers, Oral contraceptives</td>
<td>fluvoxamine nefazodone diltiazem verapamil macrolides</td>
<td>CBZ phenytoin phenobarb rifampin St John’s wort</td>
</tr>
</tbody>
</table>
**CYP2D6**

<table>
<thead>
<tr>
<th>SUBSTRATES</th>
<th>INHIBITORS</th>
<th>INDUCERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>atomoxetine</td>
<td>bupropion</td>
<td>amiodarone</td>
</tr>
<tr>
<td>duloxetine</td>
<td>fluoxetine</td>
<td>cimetidine</td>
</tr>
<tr>
<td>± fluoxetine</td>
<td>± fluvoxamine</td>
<td>methadone</td>
</tr>
<tr>
<td>± mirtazapine</td>
<td>paroxetine</td>
<td>quinidine</td>
</tr>
<tr>
<td>paroxetine</td>
<td>± sertraline</td>
<td>Ritonavir et al</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>moclobemide</td>
<td></td>
</tr>
<tr>
<td>2° &amp; 3° tricyclics (hydroxylation)</td>
<td>fluphenazine</td>
<td></td>
</tr>
<tr>
<td>trazodone</td>
<td>haloperidol</td>
<td></td>
</tr>
<tr>
<td>± clozapine</td>
<td>perphenazine</td>
<td></td>
</tr>
<tr>
<td>haloperidol</td>
<td>thioridazine</td>
<td></td>
</tr>
<tr>
<td>fluphenazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>perphenazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>risperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thioridazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>codeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mexiletine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC antiarrhythmics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β blockers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 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

### Inducers
- CBZ
- phenobarbital
- phenytoin
- dexamethasone
- rifampin
# INHIBITION PROFILES

<table>
<thead>
<tr>
<th>POTENCY</th>
<th>CYP2D6</th>
<th>CYP3A4,5,7</th>
</tr>
</thead>
<tbody>
<tr>
<td>highest</td>
<td>quinidine&lt;br&gt;paroxetine&lt;br&gt;fluoxetine&lt;br&gt;bupropion</td>
<td>ketoconazole&lt;br&gt;clarithromycin&lt;br&gt;nefazodone</td>
</tr>
<tr>
<td>intermediate</td>
<td>sertraline</td>
<td>fluvoxamine</td>
</tr>
<tr>
<td>lowest</td>
<td>fluvoxamine&lt;br&gt;nefazodone&lt;br&gt;venlafaxine&lt;br&gt;erythromycin&lt;br&gt;ketoconazole</td>
<td>sertraline&lt;br&gt;desmethylsertraline</td>
</tr>
</tbody>
</table>
INHIBITORS

- TCAs, MAOIs
- bupropion
- fluoxetine
- fluvoxamine
- paroxetine ± sertraline
- nefazodone

- antipsychotics
- acute ethanol
- disulfiram
- methylphenidate
- diltiazem
- verapamil
- valproate

-azole antifungals
- chloramphenicol
- ciprofloxacin
- cotrimoxazole
- macrolides
- metronidazole

-TCAs, MAOIs
- fluoxetine
- fluvoxamine
- paroxetine
- ± sertraline
- nefazodone

- barbiturates
- carbamazepine
- phenytoin
- primidone

- cigarette smoke
- chronic ethanol

- allopurinol
- cimetidine
- omeprazole
- phenylbutazone
- propranolol
- propoxyphene
- quinidine
- allopurinol
- cimetidine
- omeprazole
- phenylbutazone
- propranolol
- propoxyphene
- quinidine

- disulfiram
- methylphenidate
- diltiazem
- verapamil
- valproate

- isoniazid
- rifampin
- glutethimide
- omeprazole

- TCAs, MAOIs
- bupropion
- fluoxetine
- fluvoxamine
- paroxetine ± sertraline
- nefazodone

- barbiturates
- carbamazepine
- phenytoin
- primidone

- cigarette smoke
- chronic ethanol

- allopurinol
- cimetidine
- omeprazole
- phenylbutazone
- propranolol
- propoxyphene
- quinidine

- disulfiram
- methylphenidate
- diltiazem
- verapamil
- valproate

- 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

<table>
<thead>
<tr>
<th>Group</th>
<th>Protein binding</th>
<th>Hepatic elimination</th>
<th>Renal elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubes</td>
<td>(=)</td>
<td>(↑)</td>
<td>(↑)</td>
</tr>
<tr>
<td>Elderly</td>
<td>(=)</td>
<td>(= ↓)</td>
<td>↓</td>
</tr>
<tr>
<td>Pregnant</td>
<td>(=↓)</td>
<td>(= ↓ ↑)</td>
<td>↑</td>
</tr>
<tr>
<td>Manic</td>
<td>(=)</td>
<td>(=)</td>
<td>(↑)</td>
</tr>
<tr>
<td>Renal d.</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Liver d.</td>
<td>(= ↓)</td>
<td>↓</td>
<td>(= ↓)</td>
</tr>
</tbody>
</table>
# MOOD STABILIZER AND ANTICONVULSANT METABOLISM

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SUBSTRATE OF</th>
<th>INDUCES / INHIBITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>lithium</td>
<td>renal excretion</td>
<td>-</td>
</tr>
<tr>
<td>carbamazepine</td>
<td></td>
<td>induces 3A4,5,7 ...</td>
</tr>
<tr>
<td>valproate</td>
<td>3A4, 3A5-7</td>
<td>weak inhibitor</td>
</tr>
<tr>
<td></td>
<td>conjugation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β-hydroxylation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P450 oxidation</td>
<td>mildly self</td>
</tr>
<tr>
<td></td>
<td></td>
<td>induce 3A4,5,7, ...</td>
</tr>
<tr>
<td>phenytoin</td>
<td>2C9/10, ± 2C19</td>
<td>induces 3A4,5,7, ...</td>
</tr>
<tr>
<td>barbiturates</td>
<td>2C19</td>
<td>mildly self</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>UGT1A4?</td>
<td>-</td>
</tr>
<tr>
<td>gabapentin</td>
<td>renal excretion</td>
<td>-</td>
</tr>
</tbody>
</table>
LITHIUM

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

<table>
<thead>
<tr>
<th>Decreased by:</th>
<th>Not changed by:</th>
<th>Increased by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>thiazides</td>
<td>amiloride</td>
<td>acetazolamide</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>furosemide</td>
<td>mannitol</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>ASA</td>
<td>aminophylline</td>
</tr>
<tr>
<td>dehydration</td>
<td>sulindac</td>
<td>caffeine</td>
</tr>
<tr>
<td>elderly</td>
<td></td>
<td>theophylline</td>
</tr>
<tr>
<td>renal disease</td>
<td></td>
<td>pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mania</td>
</tr>
</tbody>
</table>
CARBAMAZEPINE

- Erratic absorption; F = 80%
- 75% bound; V = 1 L / kg
- \( \text{t1/2} = 24 \text{ h} \); \( \text{Cl} = 25 \text{ mL / min} \) (pre-induction)
  \( \text{t1/2} = 8 \text{ h} \); \( \text{Cl} = 75 \text{ mL / min} \) (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

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

↓ CBZ LEVELS WITH
CARBAMAZEPINE* (++)
FELBAMATE (+)
PHENOBARBITAL* (++)
PHENYTOIN* (++)
PRIMIDONE (++)

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

↓ CBZ-E LEVELS WITH
carbamazepine (+)
phenobarbital (+)
phenytoin (+)
primidone (+)

↓ CBZ-D LEVELS WITH
carbamazepine (+)
phenobarbital (+)
phenytoin (+)
primidone (+)

*

## Carbamazepine Decreases Levels of Other Drugs

*(A Partial List)*

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Anxiolytics/Sedatives</th>
<th>Anticonvulsants</th>
<th>Antimicrobials</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td><em>Alprazolam (?)</em></td>
<td>Carbamazepine</td>
<td>Caspofungin</td>
<td><em>Hormonal contraceptives</em></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Buspirone</td>
<td>Ethosuximide</td>
<td>Doxycycline</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Mirtazapine (?)</td>
<td><em>Clonazepam</em></td>
<td>Felbamate</td>
<td></td>
<td>Mifepristone</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Midazolam</td>
<td><em>Lamotrigine</em></td>
<td></td>
<td>Prednisolone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Stimulants</th>
<th>Antivirals</th>
<th>Antivirals</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Methylphenidate</td>
<td>Delavirdine</td>
<td><em>Dihydropyridine CCBs</em></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Modafinil</td>
<td>Protease inhibitors</td>
<td>Oxiracetam (?)</td>
<td></td>
</tr>
<tr>
<td>Fluphenazine (?)</td>
<td></td>
<td></td>
<td><em>Paclitaxel</em></td>
<td>Bepridil</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
<td>Quinidine</td>
<td>Dihydropyridine CCBs</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
<td>Remacemide (?)</td>
<td>Oxalacatam (?)</td>
</tr>
<tr>
<td>Quetiapine (?)</td>
<td></td>
<td></td>
<td><em>Repaglinide</em></td>
<td>Quinidine</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
<td>Teophylline (?)</td>
<td>Remepridomine (?)</td>
</tr>
<tr>
<td>Thiothixene (?)</td>
<td></td>
<td></td>
<td></td>
<td>Thoraloralyroid hormones</td>
</tr>
</tbody>
</table>

| Zopiclone?       |                       |                 |               |                       |

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Analgesics</th>
<th>Immunosuppressants</th>
<th>Muscle Relaxants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Alfentanil</td>
<td>Cyclosporine (?)</td>
<td><em>Vecuronium</em></td>
</tr>
<tr>
<td>Clolazine</td>
<td>Buprenorphine</td>
<td>Sirolimus</td>
<td>Doxacurium</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Fentanyl (?)</td>
<td>Tacrolimus</td>
<td>Pancuronium</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
<td>Rapacuronium</td>
</tr>
<tr>
<td>Quetiapine (?)</td>
<td></td>
<td></td>
<td>Rucuronium</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
<td>Thoraloralyroid</td>
</tr>
<tr>
<td>Thiothixene (?)</td>
<td>Levobupivacaine</td>
<td></td>
<td>hormones</td>
</tr>
</tbody>
</table>

| Ziprasidone      | Methadone             |                   |                 |
|                  | Tramadol              |                   |                 |

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Analgesics</th>
<th>Immunosuppressants</th>
<th>Muscle Relaxants</th>
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<tbody>
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<tr>
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<tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Quetiapine (?)</td>
<td></td>
<td></td>
<td>Rucuronium</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
<td>Thoraloralyroid</td>
</tr>
<tr>
<td>Thiothixene (?)</td>
<td>Levobupivacaine</td>
<td></td>
<td>hormones</td>
</tr>
</tbody>
</table>

| Ziprasidone      | Methadone             |                   |                 |
|                  | Tramadol              |                   |                 |

| Haloperidol      | Fentanyl (?)          |                   |                 |

## Selected Drugs that Increase Levels of Carbamazepine

(A Partial List)

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Calcium Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Hypolipidemics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Gemfibrozil</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>Nicotinamide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Macrolide Antibiotics</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Flurithromycin</td>
<td>Danazol</td>
</tr>
<tr>
<td>josamycin</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Ponsinomycin</td>
<td>d-Propoxyphene</td>
</tr>
<tr>
<td></td>
<td>Ritonovir (?)</td>
</tr>
<tr>
<td></td>
<td>Ticlopidine (?)</td>
</tr>
<tr>
<td></td>
<td>VPA (increases CBZ-E)</td>
</tr>
</tbody>
</table>

# CYP3A4-MEDIATED CBZ DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>CBZ →↓ DRUG</th>
<th>DRUG →↑ CBZ</th>
<th>DRUG →↓ CBZ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3° tricyclics</strong> (demethylation)</td>
<td>Fluoxetine, fluvoxamine, Nefazodone</td>
<td>CBZ phenobarbital, phenytoin (?)</td>
</tr>
<tr>
<td>Ca blockers</td>
<td>Ca blockers</td>
<td></td>
</tr>
<tr>
<td>CBZ</td>
<td>danazol</td>
<td></td>
</tr>
<tr>
<td>benzodiazepines</td>
<td>cimetidine</td>
<td></td>
</tr>
<tr>
<td>dexamethasone</td>
<td>clarithromycin, erythromycin</td>
<td></td>
</tr>
<tr>
<td>oral contraceptives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prednisolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>local anesthetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethosuximide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
VALPROATE

- 100% absorbed; $F = 100\%$
- 80 - 90% bound (saturable); $V = 0.1 - 0.2 \text{ L} / \text{ kg}$
- $t_{1/2} = 12 \text{ h}$; $C_l = 10 \text{ mL} / \text{ min}$
- 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

VPA glucuronide

50%

P450 OXIDATION

VPA

4-ene-VPA

0.3%

dehydro

2,4-diene-VPA

5%

1-oxid

3-OH-VPA

4%

2-ene-VPA

CO₂H

4-ene-VPA

3-ene-VPA

CO₂H

3,4'-diene-VPA

CO₂H

40%

Mitochondria

β OXIDATION

VPA

2-ene-VPA

[3-OH-VPA]

3-ene-VPA

2,3'-diene-VPA

3-oxo-VPA

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

<table>
<thead>
<tr>
<th>VPA →↑ DRUG</th>
<th>DRUG →↑ VPA</th>
<th>DRUG →↓ VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>ASA</td>
<td>CBZ ± lamotrigine</td>
</tr>
<tr>
<td>CBZ-E</td>
<td>cimetidine</td>
<td>phenobarbital</td>
</tr>
<tr>
<td>diazepam</td>
<td>fluoxetine</td>
<td>phenytoin</td>
</tr>
<tr>
<td>ethosuximide</td>
<td>felbamate</td>
<td>rifampin</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>erythromycin</td>
<td>phenothiazines</td>
</tr>
<tr>
<td>lorazepam</td>
<td>phenobarbital</td>
<td></td>
</tr>
<tr>
<td>nortriptyline</td>
<td>phenytoin</td>
<td></td>
</tr>
<tr>
<td>phenobarbital</td>
<td>zidovudine</td>
<td></td>
</tr>
</tbody>
</table>
## KEY ISOFORMS FOR ANTIDEPRESSANT METABOLISM

<table>
<thead>
<tr>
<th>ISOFORM</th>
<th>SUBSTRATES</th>
<th>INHIBITORS</th>
<th>INDUCERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>TCAs, ± mirtaz, dulox</td>
<td>fluvoxamine</td>
<td>cigs, omep</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>± citalopram, TCAs</td>
<td>fluox, fluvox</td>
<td>rifampin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>± fluoxetine</td>
<td>bupropion, fluoxetine, fluvoxamine, ± fluvoxamine</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>± mirtazapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>paroxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>dulox/venlafaxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TCAs, trazodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4,5,7</td>
<td>± citalopram</td>
<td>fluvoxamine</td>
<td>CBZ, phenytoin, phenobarb, rifampin</td>
</tr>
<tr>
<td></td>
<td>± mirtazapine</td>
<td>nefazodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nefazodone</td>
<td>± sertraline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>reboxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sertraline, TCAs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 metabls:
amitriptyline (NORT), imipramine (DMI)
• DMI (2-OH-DMI), NORT (10-OH-NORT)  CMI
  (desmethyl-CMI), DOX (desmethyl-DOX)
• $2^\circ / 3^\circ$ amines - 2-, 8-, 10-hydroxylation [2D6]
  (rate limiting)
• $3^\circ$ 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

IMI

Active Parent Drug

2-OH-IMI

Active 2-Hydroxy Metabolite

2-Hydroxy Metabolite

2-OH-DMI

Active N-Demethyl Metabolite

DMI

Carbamazepine
Phenobarbital
Phenytoin

CIGS

SSRIs

Haloperidol
Phenothiazines

1A2, 2C19, 3A4

2D6

Rate Limiting Reaction

Glucuronides

*
SSRIs & SNRIs

- **SSRIs** - fluoxetine, sertraline, paroxetine, fluvoxamine
- **SNRI** - duloxetine, venlafaxine

↓ side effects, ↑ therapeutic index cf TCAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Paroxetine Inhibits (2D6)</th>
<th>Fluoxetine Inhibits (2D6,3A4)</th>
<th>Sertraline Metabolite (±2D6)</th>
<th>Fluvoxamine Metabolite (1A2,2C9,3A4)</th>
<th>Venlafaxine Metabolite (2D6)</th>
<th>(es)Citalopram Metabolite ±(1A2,2C19,2D6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolite</td>
<td>-</td>
<td>+</td>
<td>±</td>
<td>?</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
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** \( \rightarrow \uparrow \) **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 $\rightarrow\uparrow$ 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

<table>
<thead>
<tr>
<th>VIA 1A2</th>
<th>VIA 3A4,5,7</th>
<th>VIA 2C9/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI, IMI, CMI</td>
<td>alprazolam</td>
<td>phenytoin</td>
</tr>
<tr>
<td>maprotiline</td>
<td>diazepam</td>
<td>warfarin</td>
</tr>
<tr>
<td>clozapine</td>
<td>carbamazepine</td>
<td></td>
</tr>
<tr>
<td>olanzapine</td>
<td></td>
<td>VIA 2D6</td>
</tr>
<tr>
<td>methadone</td>
<td></td>
<td>haloperidol</td>
</tr>
<tr>
<td>caffeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>phenacetin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>theophylline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SERTRALINE

- Absorption ↑ with food
- 98% bound; $V = 20 \text{ L/kg}$
- $t_{1/2} = 26 \text{ h}; \; 50 - 200 \text{ mg/d}$
- Desmethylsertraline metabolite ($\pm$ 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; $V = 8 \text{ L} / \text{ kg}$
- $t_{1/2} = 5 \text{ h}$; $Cl = 1400 \text{ mL/min}$
- 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
- t½ = 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

<table>
<thead>
<tr>
<th></th>
<th>fluoxetine</th>
<th>sertraline</th>
<th>paroxetine</th>
<th>fluvoxamine</th>
<th>venlafaxine</th>
<th>citalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>drug t1/2</strong></td>
<td>4 d</td>
<td>26 h</td>
<td>21 h</td>
<td>16 h</td>
<td>5 h</td>
<td>35 h</td>
</tr>
<tr>
<td><strong>metab t1/2</strong></td>
<td>7 d</td>
<td>3 d</td>
<td>-</td>
<td>-</td>
<td>11h</td>
<td>-</td>
</tr>
<tr>
<td><strong>Binding</strong></td>
<td>95%</td>
<td>98%</td>
<td>95%</td>
<td>80%</td>
<td>27%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Nonlinear</strong></td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±/-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td><strong>2D6 inhib</strong></td>
<td>++</td>
<td>±</td>
<td>++</td>
<td>±/-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td><strong>3A4 inhib</strong></td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±/-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td><strong>1A2 inhib</strong></td>
<td>+</td>
<td>±</td>
<td>++</td>
<td>±/-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td><strong>2C9 inhib</strong></td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±/-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td><strong>2C19 inhib</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±/-</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>
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: $t_{1/2}$ 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

BUPROPION + CYP2B6 → H-BUP (306U73)

BUPROPION

CBZ → H-BUP (306U73)

CBZ + CYP2B6 → T-BUP (494U73)

T-BUP (494U73) + VPA → MCBA

MCBA

CBZ → E-BUP (17U67)

E-BUP (17U67) + VPA → MCBA

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
  – 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; $V = 1 \text{ L} / \text{ kg}$
- $t_{1/2} = 4 \text{ h}$; $Cl = 120 - 200 \text{ mL/ min}$
- 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 (↓ 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

<table>
<thead>
<tr>
<th>ANTIHISTAMINES METABOLIZED VIA 3A3/4</th>
<th>DRUG $\rightarrow$ ↑ ANTIHISTAMINE VIA 3A3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>loratadine (Claritin)</td>
<td>ketoconazole</td>
</tr>
<tr>
<td>cetirizine (Zyrtec)</td>
<td>itraconazole</td>
</tr>
<tr>
<td>fexofenadine (Allegra)</td>
<td>fluconazole</td>
</tr>
<tr>
<td></td>
<td>erythromycin</td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
</tr>
<tr>
<td></td>
<td>troleandomycin</td>
</tr>
<tr>
<td></td>
<td>nefazodone ?</td>
</tr>
<tr>
<td></td>
<td>fluvoxamine ?</td>
</tr>
</tbody>
</table>
MIRTAZAPINE

- F = 50%; 85% bound; V = 4 L / kg
- t1/2 = 30 h; men 26 h, women 37 h
- Cl = 500 mL / min
- 15 - 45 mg / d; 40 - 120 ng / mL
- 2D6 > 1A2 → 8-hydroxy-MIRT
  3A → N-desmethyl-MIRT, N-oxide-MIRT
- N-desmethyl-MIRT metabolite
  1/10 activity, 1/3 plasma level of MIRT
- No clinically significant enzyme inhibition
- Sedation, dizziness, ↑ weight, ↑ cholesterol
- 0.1% agranulocytosis; 2% LFTs > 3 x ULN
# ANXIOLYTIC METABOLISM

<table>
<thead>
<tr>
<th>CLASS / DRUG</th>
<th>SUBSTRATE OF</th>
<th>INHIBITED BY</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-KETO</td>
<td>2C19, 3A4</td>
<td>fluoxetine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluvoxamine</td>
</tr>
<tr>
<td>clorazepate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>flurazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIAZOLO</td>
<td>3A4</td>
<td>fluoxetine</td>
</tr>
<tr>
<td>alprazolam</td>
<td></td>
<td>fluvoxamine</td>
</tr>
<tr>
<td>triazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-NITRO</td>
<td>N-reduction (3A4)</td>
<td>nefazodone</td>
</tr>
<tr>
<td>clonazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitrazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-HYDROXY</td>
<td>Conjugation UGTs</td>
<td></td>
</tr>
<tr>
<td>lorazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>temazepam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BENZODIAZEPINES

- 100% absorbed (↓ with antacid)
- 95% bound; $V = 1 \text{ L / kg}$
- $t_{1/2}$: short ($< 6 \text{ h}$) triaz, cloraz, fluraz
  intermed ($6-20 \text{ h}$) 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 ($6-20 \text{ h}$) desmethylchloridiazepoxide
  long ($> 20 \text{ h}$) desmethyldiazepam
  desalkyflurazepam
- Kinetic interactions: 2-keto (+), triazolo (+)
  7-nitro (±), 3-hydroxy (-)
- High therapeutic indices
# BENZODIAZEPINES

<table>
<thead>
<tr>
<th>2-KETO</th>
<th>TRIAZOLO</th>
<th>7-NITRO</th>
<th>3-HYDROX</th>
</tr>
</thead>
<tbody>
<tr>
<td>clorazepate</td>
<td>alprazolam</td>
<td>clonazepam</td>
<td>lorazepam</td>
</tr>
<tr>
<td>diazepam</td>
<td>triazolam</td>
<td>nitrazepam</td>
<td>oxazepam</td>
</tr>
<tr>
<td>flurazepam</td>
<td></td>
<td></td>
<td>temazepam</td>
</tr>
</tbody>
</table>

- **N-dealk [2C19] - 3-hydrox [3A4]**
  - active, long t1/2 metab 
  - + kinetic ints

- **4-hydrox [3A4], α-hydrox [3A4]**
  - active, short t1/2 metab (alpraz)
  - + kinetic ints

- **N-reduction**
  - inactive metab
  - ± kinetic ints

- **direct conjugation**
  - inactive metab
  - ± 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],
α-hydroxylation [3A4]

↑ metabolism with:
CBZ

↓ metabolism with:
fluoxetine, fluvoxamine
nefazodone, BCPs
erthromycin, ketoconazole
cimetidine, propoxyphene
DIAZEPAM METABOLISM

CARBAMAZEPINE, PHENOBARBITAL, PHENYTOIN, RIFAMPIN

N-DEALKYLATION

2C19 (3A4)

N-DESMETHYL-DIAZEPAM

ACTIVE 2-KETO-BZ

BCPs, CIMETIDINE, FLUOXETINE, FLUVOXAMINE, OMEPRAZOLE

3-HYDROXYLATION

3A4 (2C19)

OXAZEPAM

ACTIVE 3-HYDROXY-BZ (DIRECTLY CONJUGATED)
## ANTIPSYCHOTIC METABOLISM

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SUBSTRATE OF</th>
<th>INHIBITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>haloperidol</td>
<td>2D6</td>
<td>2D6</td>
</tr>
<tr>
<td>fluphenazine</td>
<td>2D6, +/-1A2</td>
<td>2D6</td>
</tr>
<tr>
<td>perphenazine</td>
<td>2D6</td>
<td>2D6</td>
</tr>
<tr>
<td>thioridazine</td>
<td>2D6</td>
<td>2D6</td>
</tr>
<tr>
<td>clozapine</td>
<td>1A2, ± 2D6</td>
<td>-</td>
</tr>
<tr>
<td>risperidone</td>
<td>2D6, 3A4</td>
<td>-</td>
</tr>
<tr>
<td>olanzapine</td>
<td>UGTs, 1A2</td>
<td>-</td>
</tr>
<tr>
<td>ziprasidone</td>
<td>Aldehyde ox, 3A4, ± 1A2</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2D6, 3A4</td>
<td>-</td>
</tr>
<tr>
<td>quetiapine</td>
<td>3A4</td>
<td>-</td>
</tr>
</tbody>
</table>
TYPICAL ANTIPSYCHOTICS

• F = 20 - 80%
• absorption ↓ with antacid
• 80 - 95% bound; V = 10 - 40 L / kg
• t₁/₂ = 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

<table>
<thead>
<tr>
<th>DRUG → ↑ AP</th>
<th>DRUG → ↓ AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>tricyclics</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>phenobarbital</td>
</tr>
<tr>
<td>β blockers</td>
<td>phenytoin</td>
</tr>
<tr>
<td>cimetidine</td>
<td>cigarettes</td>
</tr>
<tr>
<td></td>
<td>rifampin</td>
</tr>
</tbody>
</table>

AP → ↑ DRUG

tricyclics
CLOZAPINE

- 100% absorbed; $F = 70\%$
- 97% bound; $V = 5 \text{ L} / \text{ kg}$
- $t_{1/2} = 12 \text{ h}; \text{ CI} = 750 \text{ mL} / \text{ min}$
- 50 - 900 mg / d; 100 - 600 ng / mL
- Desmethylclozapine 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 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) is substrate CYP3A4
- Risperidone is CYP2D6 substrate
- Carbamazepine → ↓ risperidone
- Fluoxetine → ↑ 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 $\rightarrow \downarrow$ 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)
• Inactive sulfoxide metabolite via CYP3A4
• PHT, thioridazine → ↓ quetiapine
• Quetiapine → ↑ warfarin
• Well tolerated with lithium
• No effect on lithium levels
ZIPRASIDONE

- 60% absorbed with food (30% unfed)
- 99% bound; $V = 1.5 \text{ L/kg}$
- $t_{1/2} = 6.6 \text{ h}; \text{Cl} = 525 \text{ mL/min}$
- 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 L / kg
- t1/2 = 75 h
- 10 - 30 mg / d
- Metabolized by CYP2D6, CYP3A4
- Active dehydro-aripiprazole metabolite (t1/2 = 94 h)
- carbamazepine $\rightarrow$ ↓ aripiprazole
- ketoconazole $\rightarrow$ ↑ aripiprazole
- quinidine $\rightarrow$ ↑ aripiprazole
- Not affected by lithium or VPA
# ANTICONVULSANT ELIMINATION

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SUBSTRATE OF</th>
<th>INDUCES / INHIBITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine</td>
<td>3A4</td>
<td>induces 3A4, UGTs</td>
</tr>
<tr>
<td>valproate</td>
<td>conj&gt;α-oxid&gt;P450oxid</td>
<td>weak inhibitor</td>
</tr>
<tr>
<td>felbamate</td>
<td>renal&gt;conj,oxid</td>
<td>induces 3A4</td>
</tr>
<tr>
<td>gabapentin</td>
<td>renal excretion</td>
<td></td>
</tr>
<tr>
<td>lamotrigine</td>
<td>conjugation</td>
<td>Weak inducer UGTs</td>
</tr>
<tr>
<td>topiramate</td>
<td>renal&gt;hydrox,hydrol,conj</td>
<td>± inhibits 2C19,</td>
</tr>
<tr>
<td>tiagabine</td>
<td>3A4, conjugation</td>
<td>induces 3A4</td>
</tr>
<tr>
<td>oxcarbapazine</td>
<td>reduction</td>
<td></td>
</tr>
<tr>
<td>vigabatrin</td>
<td>renal excretion</td>
<td></td>
</tr>
<tr>
<td>zonisamide</td>
<td>3A4 (reduction)</td>
<td></td>
</tr>
</tbody>
</table>
GABAPENTIN

- $F = 60\%$
- Absorption less with doses > 900 mg
- 0% bound; $V = 1 \text{ L} / \text{ kg}$
- $t_{1/2} = 6 \text{ h}; \ Cl = 120 \text{ mL} / \text{ min} = \text{ GFR}$
- 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 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 →↑ CBZ neurotoxicity (dynamic vs ↑ CBZ-E)
- LTG → ± ↓ VPA
- VPA, ± sertaline → ↑ LTG
- CBZ, PHT, PB, PRIM, BCPs → ↓ LTG
## Lamotrigine Titration Influenced by Valproate and Carbamazepine

**Table: Lamotrigine Titration in Adults**

<table>
<thead>
<tr>
<th>Week</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 mg</td>
</tr>
<tr>
<td>2</td>
<td>25 mg</td>
</tr>
<tr>
<td>3</td>
<td>50 mg</td>
</tr>
<tr>
<td>4</td>
<td>50 mg</td>
</tr>
<tr>
<td>Week 5 onward</td>
<td>Add 50-100 mg/wk as clinically indicated</td>
</tr>
<tr>
<td>Maintenance</td>
<td>100-400 mg</td>
</tr>
</tbody>
</table>

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

---

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 monoR$\times$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 $\rightarrow \downarrow$ ethinyl estradiol (CYP3A4 modest induction)
- OXC $\rightarrow \uparrow$ PHT (CYP2C19 inhibition)
- Low therapeutic index (neurotoxicity)
ZONISAMIDE

- 15% bound
- $t_{1/2} = 60$ h with monoRx
  $t_{1/2} = 30$ h with inducers
- $Cl = 20$ mL / min
- Reduced to 2-sulfamoylacetylphenol (SMAP)
- 100 mg/d → ↑ 100 mg/d q 2wks -up to 300-600 mg/d
- CBZ, PHT, PB → ↓ ZNS; LTG → ↑ ZNS
LEVETIRACETAM

- $F = 100\%, < 10\%$ bound
- $66\%$ excreted unchanged
- $24\%$ hydrolyzed to inactive metabolite (ucb L057)
- $t_{1/2} = 8\, h$
- $Cl = 40\, mL / min$
- $1000\, mg/d \rightarrow 1000\, mg/d$ 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 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
REFERENCES


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
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
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
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
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