# Drug-Drug Interactions in Psychiatry

John J. Miller, M.D.
Medical Director, Brain Health
Exeter, NH

## Acknowledgement

Some of the slides used in this presentation were created by Jessica R. Oesterheld, MD. The primary reference used in the development of this presentation was: Drug Interaction Principles for Medical Practice, Second Edition; Cozza K, Armstrong S, and Oesterheld J.; American Psychiatric Publishing, Inc.; Copyright 2003.

## Objectives

- Review the different types of Drug-Drug Interactions
- Appreciate the differences among the Phase I Cytochrome P-450 enzymes, Phase II conjugation reactions and P-Glycoproteins in Drug-Drug Interactions
- Describe some of the common Drug-Drug Interactions one needs to consider when prescribing psychotropic medication

## Types of Drug-Drug Interactions

- Absorption (gut, skin)
- Protein Binding
- P- Glycoproteins
- Phase I Metabolism = CYP450 Enzyme System
- Phase II Metabolism = Conjugation
  - Glucuronidation, Sulfation and Methylation
- Pharmacodynamic
- Excretion (urine, bile and gut)

# Differing Metabolic Pathways

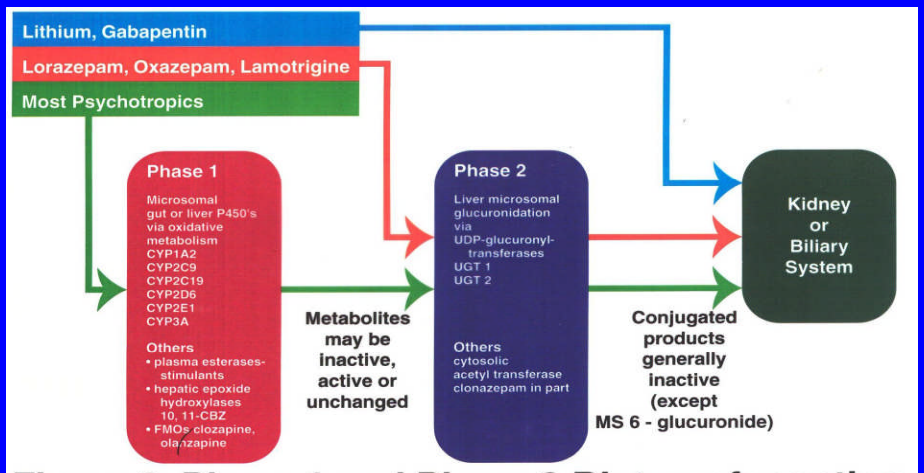



Figure 2. Phase 1 and Phase 2 Biotransformation

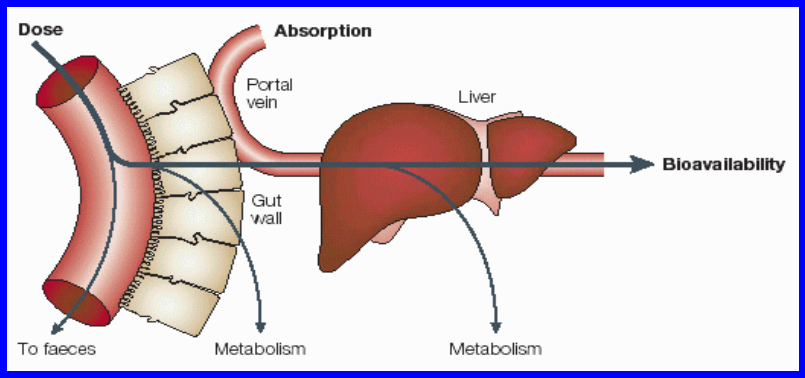
# Types of Drug-Drug Interactions

## Absorption

**(most occur in the gut):**

- Food
- gastric pH
- OTCs
- other medications
- Loss of gut flora
- Mechanical blockade

Uptake of an orally administered drug proceeds after the stomach passage via the small intestine.
In the gut and liver, a series of metabolic transformation occurs.




# Types of Drug-Drug Interactions

## Protein Binding

Not as clinically relevant as previously believed.

Properties of a drug that predict clinically relevant displacement by protein binding:
- low clearance drugs
- low therapeutic index
- small volume of distribution

Examples: warfarin, tolbutamide, phenytoin

## Protein Binding and Urinary Excretion of SRIs

| Drug | % Protein Bound | % Urinary Excretion | Half-Life |
|---|---|---|---|
| fluoxetine | 94 | <2.5 | 14 days |
| S-sertraline | 98 | <1 | 26 hours |
| R-paroxetine | 95 | <2 | 21 hours |
| fluvoxamine | 77 | <5 | 15 hours |
| venlafaxine | 27 | 4.6 | 5 hours |
| D-M-venlafaxine | 30 | 29 | 11 hours |
| citalopram | 80 | 10.5 | 35 hours |
| S-citalopram | 56 | 18* | 29 hours |

The Pharmacological Basis of Therapeutics; Goodman & Gilman; 10th Edition; 2001
*From Physician's Desk Reference; 2004; page 1302.

## Protein Binding of Atypical Antipsychotics

| Atypical | % Protein Bound |
|---|---|
| Aripiprazole (Abilify) | 99% |
| Clozapine (Clozaril) | 97% |
| Olanzapine (Zyprexa) | 93% |
| Quetiapine (Seroquel) | 83% |
| Risperidone (Risperdal) | 90% |
| Ziprasidone (Geodon) | 99% |

2005 Physicians' Desk Reference

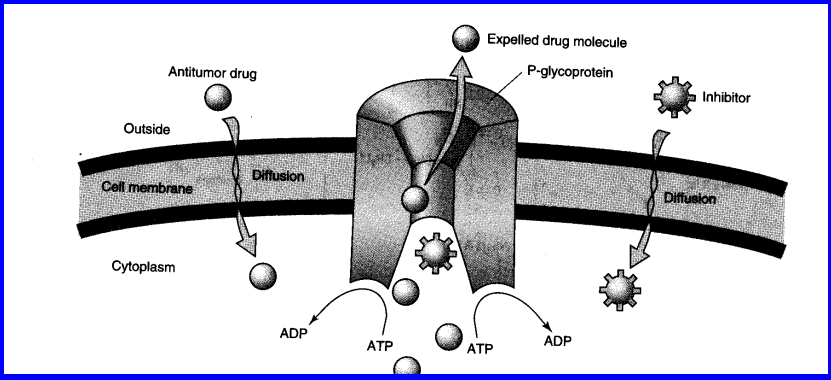
# Types of Drug-Drug Interactions

## P- Glycoproteins

(efflux transporters)

Multidrug resistance (MDR) was observed over 40 years ago in certain types of cancer (leukemia, breast cancer). These cancer cells were found to over express a protein from the MDR1 gene that would actively transport some cancer drugs out of the cancer cell. This protein used ATP as an energy source, and is membrane based. It has been named P (permeability) - glycoprotein.

# P (permeability) -Glycoprotein



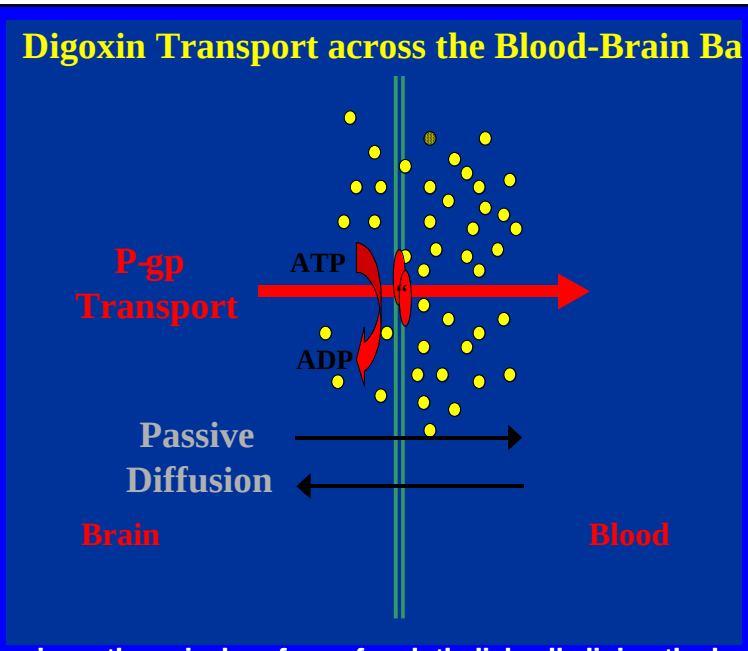
## P- Glycoproteins

Located in the jejunum, colon,renal proximal tubules, biliary system, gonads, placenta, and blood brain barrier.

- Drug interactions include:
  - None
  - Substrate
  - Inhibitor
  - Inducer
  - Substrate/Inhibitor
  - Substrate/Inducer

## P- Glycoproteins

- Digoxin is a well studied substrate
- P-Glycoprotein inhibitors (quinidine) increases digoxin levels.
- P-Glycoprotein inducers (rifampin, St. John's wort) decrease digoxin levels.



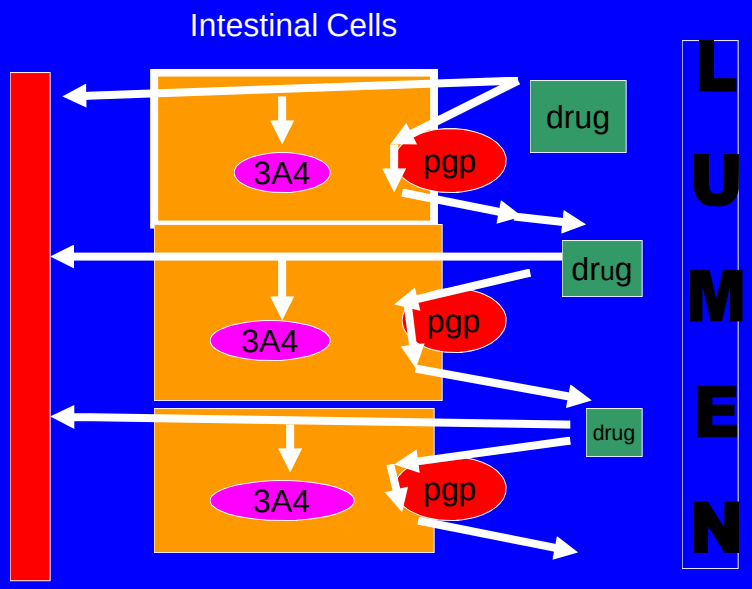

Pgp is on the apical surface of endothelial cells lining the brain capillaries that forms BBB (From David Flockhart)

## Clinical relevance of a P-gp inhibitor

The anti-diarrheal drug loperamide is usually prevented from entering the CNS because it is a P-gp substrate on the BBB. In the presence of the P-gp inhibitor quinidine at sufficient dosage, a patient will get the CNS side effect of respiratory depression due to the increased CNS penetration of loperamide (Sadeque and Wandel 2000).

## CYP450 3A4 and P-gps work together in the gut

- Many substrates of P-gps are also substrates of CYP450 3A4
- Some drugs are both P-gp and CYP450 3A4 inhibitors (e.g., erythromycin, cyclosporin)
- Some drugs are both P-gp and CYP450 3A4 inducers (e.g., St John's wort, rifampin)
- In the small intestine, P-gps efflux compounds back to the lumen, where it is then reabsorbed; this "shuttle" leads to increased "exposure" of compounds to CYP3A4 and maximizes their activity




P-gps in "front"- with repeated shuttles of absorption/efflux

# Types of Drug-Drug Interactions

## Phase I Metabolism

### CYP450 Enzyme System

**Nomenclature:**
Cyto = microsomal vesicles
Chrome = colored
P = protein
450 = absorb light at 450 nanometer wavelength
2 = family = 40-55% homologous amino acid sequence
D = subfamily > 55% homologous amino acid sequence
6 = single gene

# CYP450 Enzyme System

**An oxidase system:**

N-dealkylation
O-dealkylation
hydroxylation
N-oxidation
S-oxidation
deamination

## CYP450 Enzyme System

over 40 human CYP450 enzymes identified

Ninety percent of human drug oxidation is accomplished by six CYP450 enzymes:

| | |
|---|---|
| 1A2 | 2D6 |
| 2C9 | 2E1 |
| 2C19 | 3A4 |

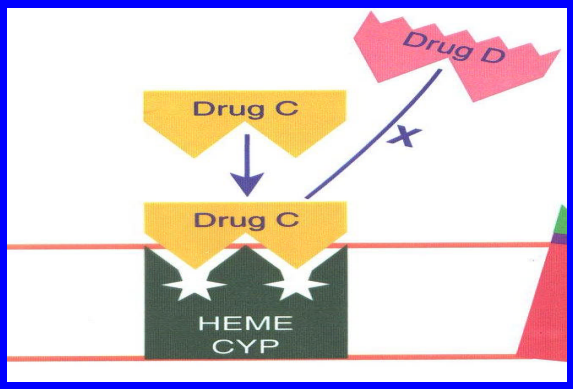
All 6 have genetic polymorphisms

## CYP450 Enzyme System

Drug interactions include:

- None
- Substrate
- Inhibitor
- Inducer
- Substrate/Inhibitor
- Substrate/Inducer

# Inhibition



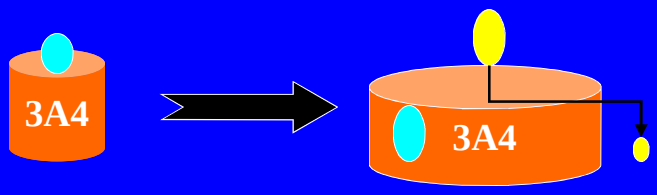

Drug D = substrate

Drug C = inhibitor
or
substrate/inhibitor

Drug-Drug Interaction occurs almost immediately.
It doesn't matter which drug is added first.

# Induction

Drug D = inducer or substrate/inducer
Drug C = substrate




Induction of 3A4 by drug D lowers concentration of drug C.

---

With induction, it matters which drug is first:
DDI will take some time to develop if drug D is added second;
DDI will occur immediately if it is already present for several days.

## CYP450 Drug-Drug Interactions

- Fluoxetine/paroxetine both potent inhibitors of CYP2D6.
- Desipramine/nortriptyline primarily metabolized by CYP2D6.
- 1988 – reports surfaced about cardiotoxicity in patients who were treated with both fluoxetine and desipramine.
- Began intensive research into the liver's CYP450 enzyme system.

## CYP450 Drug-Drug Interactions

- Terfenadine is a pro-drug that is rapidly metabolized by CYP3A4 to its active metabolite fexofenadine, which is then excreted unchanged by the kidneys.
- Terfenadine becomes arrhythmogenic as its serum levels increase.
- Ketoconazole is a VERY POTENT inhibitor of CYP3A4.
- Terfenadine plus ketoconazole polypharmacy were causal of arrhythmias and sudden death – 1997 terfenadine taken off US market.

## Serotonin Reuptake Inhibitors*

- fluoxetine (Prozac)
- clomipramine (Anafranil, a TCA)
- sertraline (Zoloft)
- paroxetine (Paxil, Paxil CR)
- fluvoxamine (Luvox)
- venlafaxine (Effexor, IR XR)
- citalopram (Celexa, Lexapro)
- duloxetine (Cymbalta)

*In order of U.S.A. market entry.

## *In Vivo* effect of SSRIs on the Major Human Cytochrome P450 enzymes*

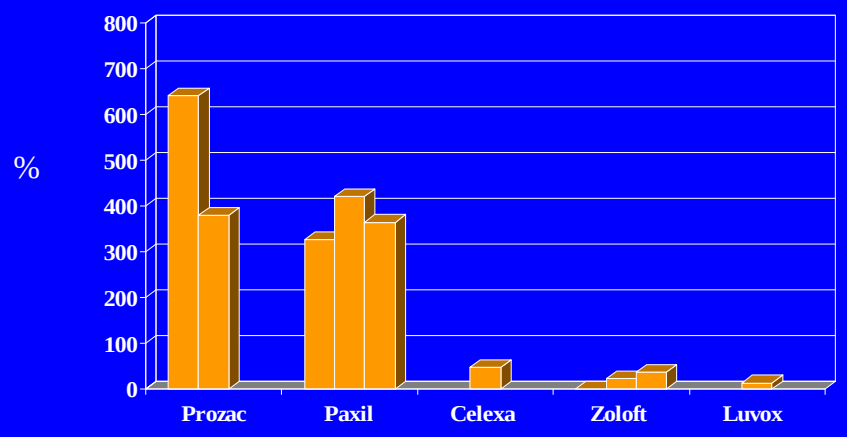
| SSRI | 1A2 | 2D6 | 2C9/10 | 2C19 | 3A3/4 |
|---|---|---|---|---|---|
| Citalopram (40mg) | - | ++ | - | - | - |
| Escitalopram (20mg) | - | ++ | - | - | - |
| Fluoxetine (20mg) | - | +++ | +++ | ++ | + |
| Fluvoxamine (150mg) | +++ | - | +++ | +++ | ++ |
| Paroxetine (20mg) | - | +++ | - | - | - |
| Sertraline (100-200mg) | - | + | - | - | - |

* ( - = <20%; + = 20%-50%; ++ = 50%-150%; +++ = >150% )

Preskorn, S; *J Psych Practice*; Vol. 9, No. 3; page 229; May 2003

## SSRIs Effect on Desipramine Levels at CYP450-2D6

% Change in plasma desipramine levels after adding an SSRI

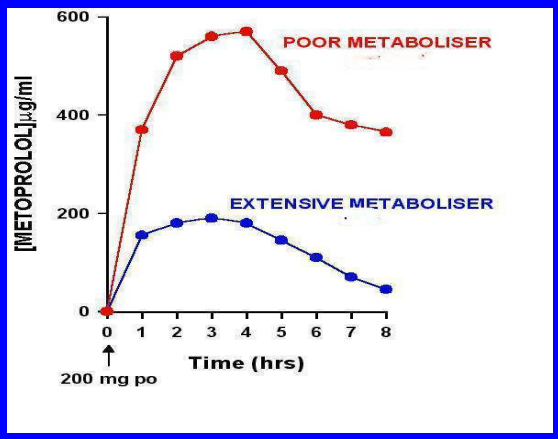



Preskorn S; "Pharmacology of SSRIs"; Clin. Pharmacokinet.; 1997; 32 Suppl. 1: 1-21

## CYP450 2D6 genetic polymorphisms – over 30 alleles

- "Extensive Metabolizer" = Normal functioning genes
- "Poor Metabolizer" = Gene defect or inactivation
- "Ultraextensive Metabolizer" = duplicate or multiple copies of the 2D6 gene
- Approximately 10% of Caucasians are poor metabolizers

## Clinical Implications of CYP2D6 variants:

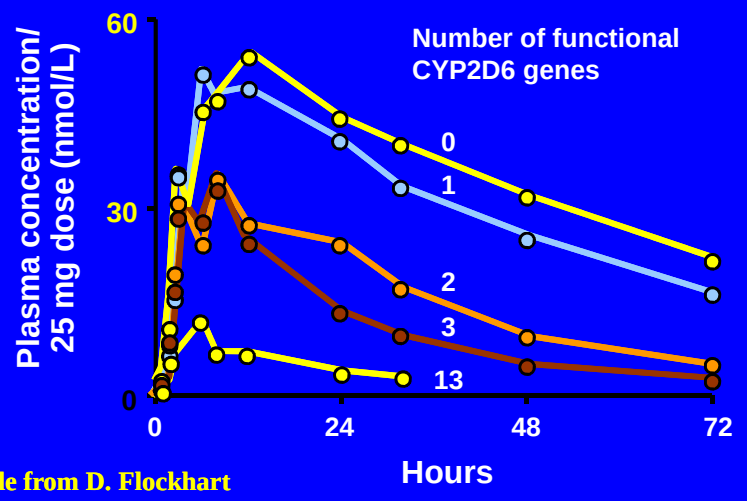



## CYP450 2D6 Polymorphisms:

**www.imm.ki.se/CYPalleles/**

| Designation | Characteristic mutation(s) | Enzyme activity | Allelic frequency (%) |
|---|---|---|---|
| *CYP2D6*1* | Wild type | Normal | |
| *CYP2D6*2* | $G_{1749}C$, $C_{2938}T$, $G_{4268}C$ substitutions | Normal | 30 |
| *CYP2D6*3* | $A_{2637}$ deletion | Deficient | 2 |
| *CYP2D6*4* | $G_{1934}A$ substitution | Deficient | 22 |
| *CYP2D6*5* | Gene deletion | Deficient | 2 |
| *CYP2D6*6* | $T_{1795}$ deletion | Deficient | 2 |
| *CYP2D6*7* | $A_{3023}C$ substitution | Deficient | 0·1 |
| *CYP2D6*8* | $G_{1846}T$ substitution | Deficient | 0·1 |
| *CYP2D6*9* | ($A_{2701}$–$A_{2703}$) or ($G_{2702}$–$A_{2704}$) deletion | Decreased | 1·5 |
| *CYP2D6*10* | $C_{188}T$, $G_{1749}C$, $G_{4268}C$ substitutions | Decreased | 1·5 |
| *CYP2D6*11* | $G_{971}C$ substitution | Deficient | 0·1 |
| *CYP2D6*12* | $G_{212}A$ substitution | Deficient | 0·1 |
| *CYP2D6*13* | Hybrid: *2D7* exon 1, *2D6* exons 2–9 | Deficient | 0·1 |
| *CYP2D6*14* | $G_{1846}A$ substitution | Deficient | 0·1 |
| *CYP2D6*15* | $T_{226}$ insertion | Deficient | 0·1 |
| *CYP2D6*16* | Hybrid: *2D7* exons 1–7, *2D6* exons 8–9 | Deficient | 0·1 |
| *CYP2D6*1* × 2 | Gene duplication | Increased | 1 |
| *CYP2D6*2* × 2 | Gene duplication | Increased | 1·5 |
| *CYP2D6*4* × 2 | Gene duplication | Deficient | 0·5 |

## Nortriptyline: 2 allele patients had greater clearance than 1 or 0 allele patients.




Slide from D. Flockhart

## CYP450 Metabolic Pathways of the Atypical Antipsychotics

| Atypical | Primary | Secondary |
|---|---|---|
| Aripiprazole | 2D6, 3A4 | - |
| Clozapine | 1A2 | 3A4, 2D6, 2C9, 2C19 |
| Olanzapine | 1A2 | 2D6 |
| Quetiapine | 3A4 | - |
| Risperidone | 2D6, 3A4 | - |
| Ziprasidone | Aldehyde oxidase | 3A4 |

Cozza, K., Armstrong, S. and Oesterheld, J.; Drug Interaction Principles For Medical Practice, Second Edition; American Psychiatric Publishing, Inc.; 2003

## Cytochrome P450 1A2

**Inhibitors**

- Fluvoxamine
- Cimetidine

**Inducers**

- Tobacco Smoke

**Substrates**

- Fluvoxamine
- Caffeine
- Theophylline
- Clozapine
- Olanzapine
- Haldol
- Acetaminophen
- Warfarin

## Cytochrome P450 3A4

**Inhibitors**

- Ketoconazole
- Nefazodone
- Fluvoxamine
- Fluoxetine (Mild)
- Erythromycin
- Cimetidine

**Inducer**

- Carbamazepine
- Modafinil
- St John's wort

**Substrates**

- Terfenadine (pro-drug)
- Pimozide (pro-drug)
- Steroids
- Sertraline
- Citalopram
- Alprazolam
- Risperidone
- Quetiapine
- Aripiprazole

## Cytochrome P450 2D6

**Inhibitors**

- Paroxetine
- Fluoxetine
- Norfluoxetine
- Cimetidine
- Bupropion
- Hydroxybupropion

**Substrates**

- Desipramine
- Venlafaxine
- Aripiprazole
- Risperidone
- Paroxetine
- Fluoxetine
- Metoprolol
- Codeine (pro-drug)
- Oxycodone
- Dextromethorphan

## Types of Drug-Drug Interactions

**Phase II Metabolism**

Conjugation

- Molecules are added to the drug making it more water soluble
  - Glucuronidation
  - Sulfation
  - Methylation

## Phase II Metabolism = Conjugation

- Glucuronidation
  - Located in the endoplasmic reticulum
  - Primary site is the liver
  - Secondary site is the gut
  - Most common and most important type of Phase II enzymes are members of the family uridine 5'-diphosphate glucuronosyltransferases (UGT's)

## Phase II Metabolism = Conjugation

- Glucuronidation
- uridine 5'-diphosphate glucuronosyltransferases (UGT's)
  - Over 1000 exogenous substrates
  - Have inhibitors and inducers
  - Nomenclature (developed in 1997) exists based on amino acid similarity
  - Examples:
    - UGT1A1
    - UGT2B4

## Phase II Metabolism = Conjugation

- Glucuronidation
- Drugs metabolized by UGT's:
  - Lorazepam, oxazepam, temazepam
  - Lamotrigine
  - Valproate
  - NSAIDs
  - Most opioids
  - Ethinyl estradiol

## UGTs-Lamotrigine Metabolism

Lamotrigine

UGT1A4 ↓ valproate inhibits

Ethinyl estradiol induces

Lamotrigine-glucuronide

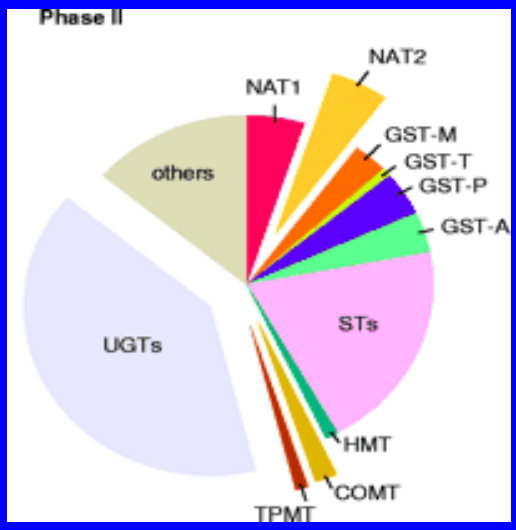
## Phase II Metabolism = Conjugation

- Sulfation (AKA sulfonation)
  - Sulfotransferases (SULT) transfer a sulfuryl group onto the drug
  - Nomenclature is similar to UGT and CYP450
  - Examples:
    - SULT1A1
    - SULT2A1

## Phase II Metabolism = Conjugation

- Methylation
  - Catechol O-Methyltransferase (COMT)
    - Discovered 70 years ago
    - Metabolizes catecholamines
  - Histamine N-Methyltransferase (HNMT)
    - Inhibitors prolong histamine acitvity and result in increased anti-inflammatory action
  - Thiopurine Methyltransferase (TPMT)

## Phase II transferases




From: Evans WE, Relling MV. Pharmacogenomics: Translating functional genomics into rational therapeutics. *Science* 286:487-491, 1999.

## Types of Drug-Drug Interactions

### Pharmacodynamic

Drug-Drug Interactions that occur due to two or more drugs effecting the same target receptor or end organ, and resulting in an increase or decrease in the pharmacological action at that receptor or end organ as compared to the activity of each drug alone.

# Pharmacodynamic DDIs

## Examples:

Addition of diphenhydramine to quetiapine will increase the overall antihistamine load, commonly increasing sedation.

Addition of benztropine to donepezil will decrease effectiveness of donepezil, as benztropine is anticholinergic, and donepezil increases acetylcholine by blocking AcetylCholinesterase enzymes.

# Types of Drug-Drug Interactions

## Excretion

renal

bile

gut

Classic example is the effect of sodium concentration or diuretics or NSAIDs on lithium levels.

## With polypharmacy - look for red flags

Be particularly vigilant if any prescription drug or herb or OTC drug has:

- a narrow therapeutic index (VPA, theophylline, carbamazepine, lithium, TCAs, opioids)
- causes serious side effects ( cardiotoxicity, rhabdomyolitis, respiratory depression, bleeding, somnolence, increased fertility)
- has a single metabolic pathway
- is a potent inhibitor or inducer (older anticonvulsants, many HIV drugs, antidepressnts, tobacco smoke, antifungals, antibiotics, St. John's wort)

## Drug-Drug Interaction Patterns

- In the presence of any new symptoms or side effects, focus in on the last medication change or dosage change
- Ask if the new symptoms or side effects occur in a time pattern consistent with a Drug-Drug Interaction
- Immediate Drug-Drug Interactions:
  - add drug to inhibitor
  - inhibitor to drug
  - drug to inducer
  - removal of inhibitor
- Delayed Drug-Drug Interactions:
  - add an inducer to drug
  - removal of an inducer

# Questions?