Drug-Drug Interactions 101 or Will It Take a 2 by 6 to Get You to Understand CYP2D6?

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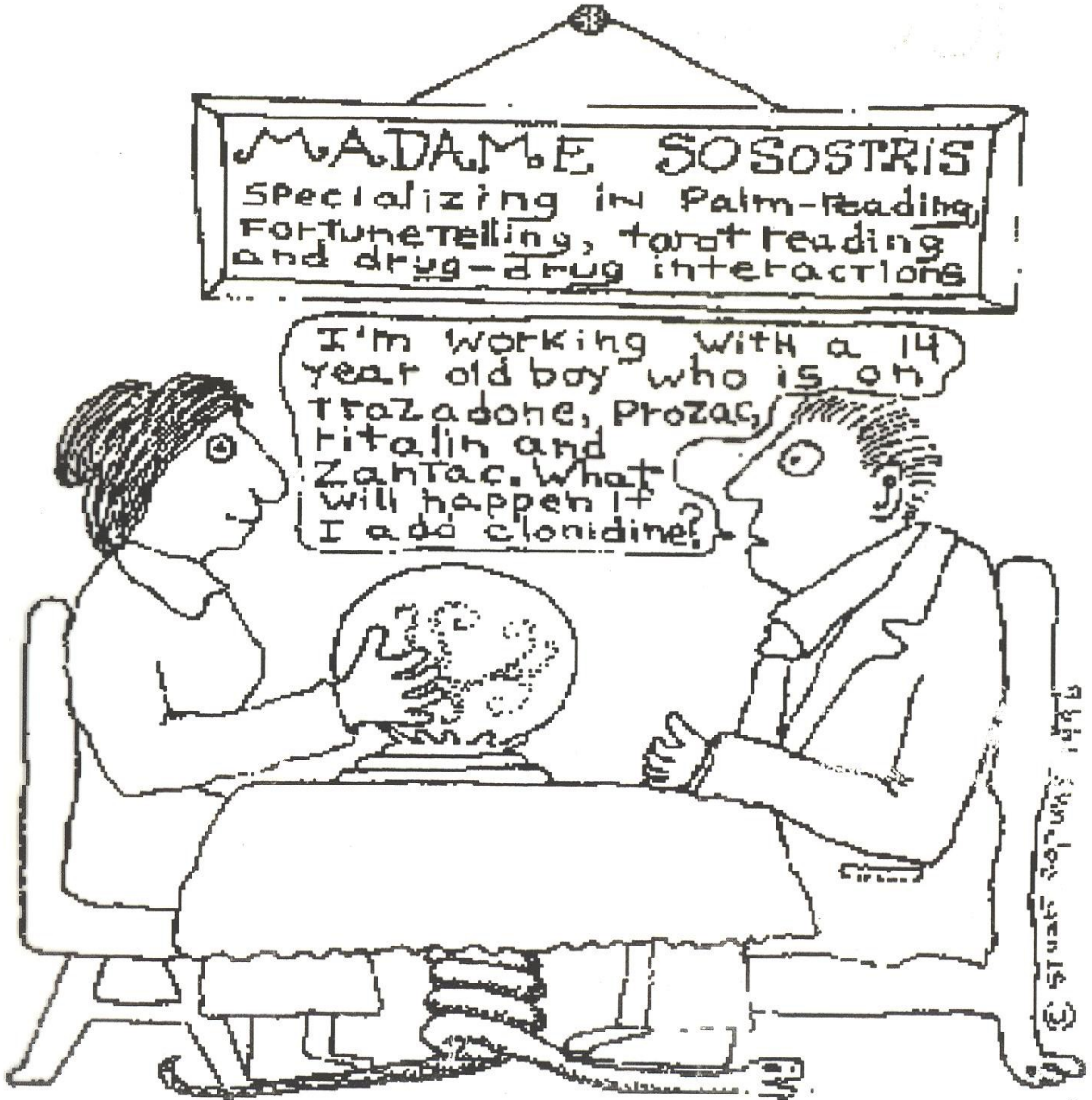

MADAME SOSOSTRIS
Specializing in Palm-Reading
Fortunetelling, tarot reading
and drug-drug interactions
I'm working with a 14 year old boy who is on Trazadone, Prozac, Ritalin and Zantac. What will happen if I add clonidine?

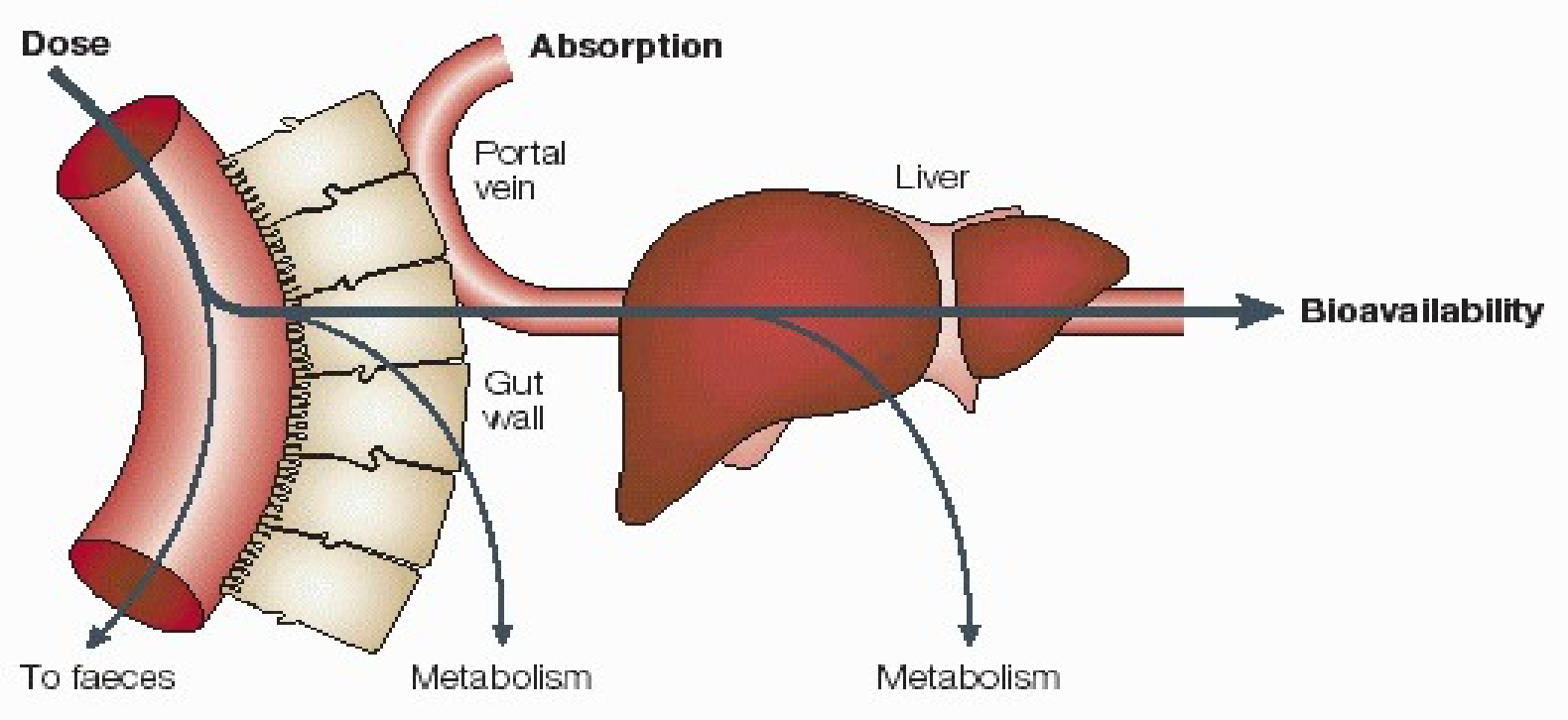
What will we do today?

- Review basic facts about metabolism of drugs
- Learn how CYP-based DDIs occur
- Learn about CYP substrates, inhibitors and inducers and genetic factors
- Learn about UGT-based drug DDIs e.g.,Lamotrigine
- Mid-talk we will look at the Psychiatric CYP Chart and do a few vignettes
- Learn to prevent possible DDIs in the real world

Metabolism

- Drugs are swallowed, pass through stomach and are generally absorbed in the small intestine-------> liver-------> systemic circulation
- At the small intestine and liver are 2 groups of docking stations with unique configurations that are metabolic facto ries responsible for Phase 1 Reactions and Phase 2 Reactions
- Drug products not transformed continue through the gut

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



Phase 1 and Phase 2 Reactions

- Phase 1 -introduces oxygen providing a “chemical handle” -> drug more “water-loving” (so it can be handled by the kidney or biliary system) and starts to inactivate it
- Phase 2 uses the handle to allow enzymes called transferases to hook up to Phase 1 products and further inactivate and make them hydrophilic: conjugation **with glucuronic acid, sulfate, acetic acid or an amino acid**

Phase I (Functionalization):

Oxidation

- Cytochrome P450
- Alcohol Dehydrogenase
- Monoamine Oxidase

Reduction

- Cytochrome P450

Hydrolysis

- Esterases
- Amidases

Phase II (Conjugation):

- Glucuronosyltransferases (UGTs)
- Acetyltransferases (NATs)
- Sulfotransferases (SULTs)
- Methyltransferases
- Glutathione Transferases
- Amino Acid Transferases

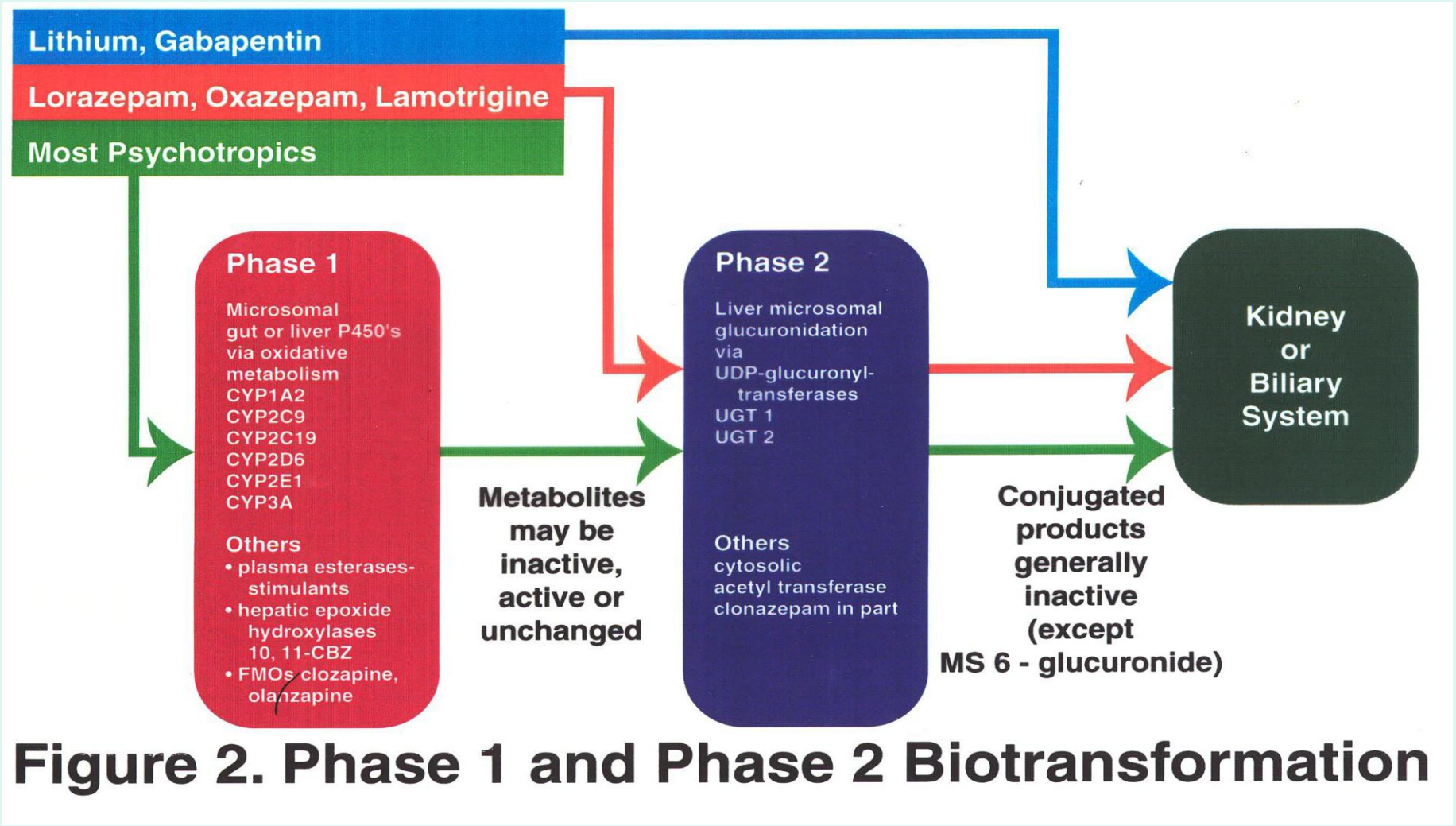


Figure 2. Phase 1 and Phase 2 Biotransformation

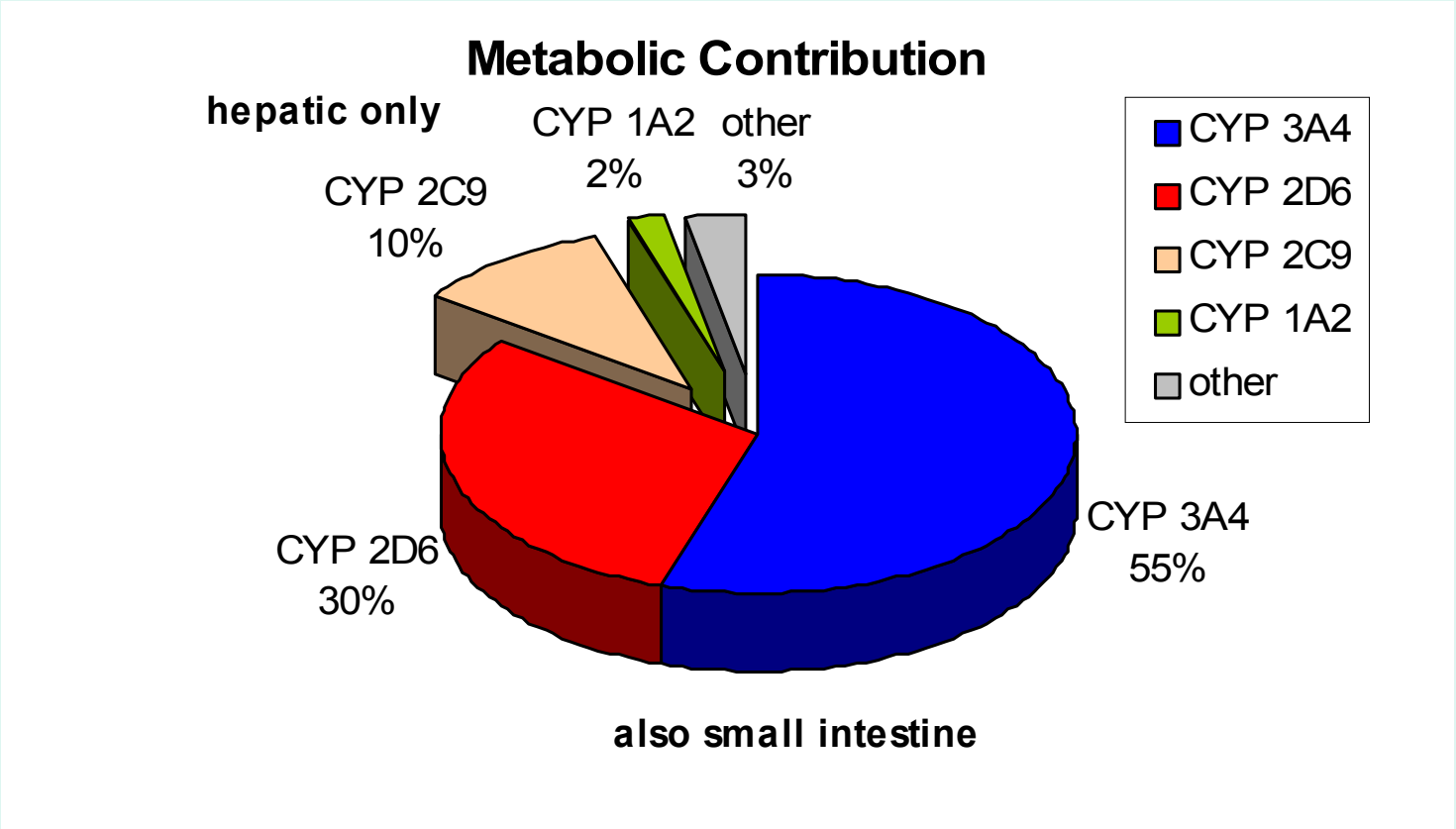
What are CYPs?

- Millions of years ago, plants developed toxins (so not to be eaten) and animal retaliated by developing metabolic factories to chew the toxins up safely
- Superfamily of heme-containing enzymes
- 2 kinds, some in mitochondria that chew up endogenous products (e.g. steroids) and those tp be discussed today in the endoplastic reticulum that chew up drugs, foods, herbals, toxins

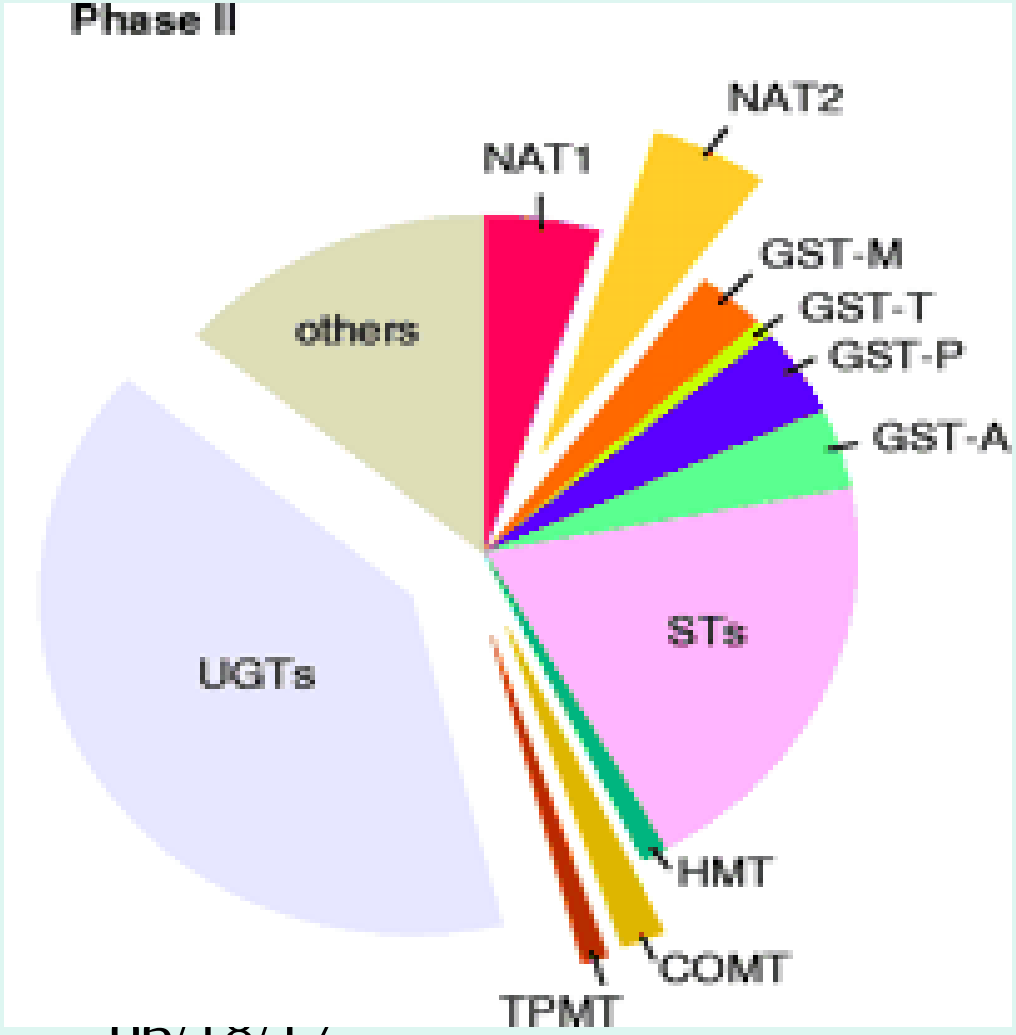

Acer platanoides
Morus alba
Quercus nigra
us deltoides
Cercis canadensis
Ulmus alata
Quercus marilandica
Celtis occidentalis
us racemosa

Cytochrome P450 enzymes

Especially CYP 3A4, CYP 2D6, and CYP 2C9 are involved in the metabolism of xenobiotics and drugs.



Phase 2 transferases (conjugation)



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

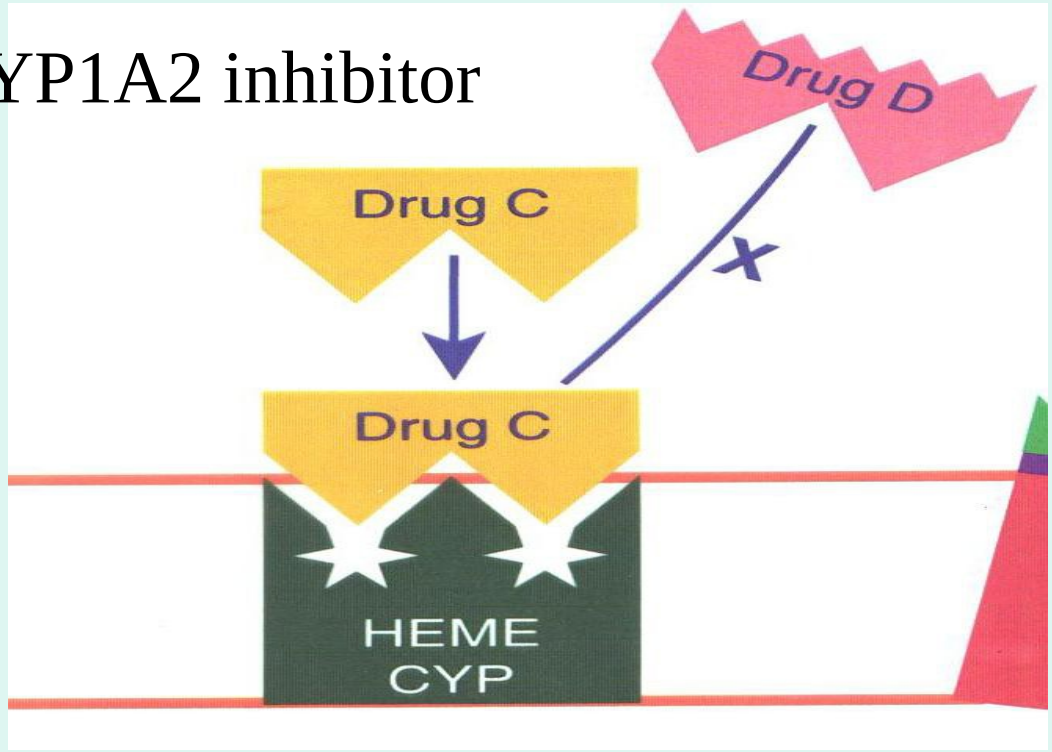
How do CYP-based DDIs occur? INHIBITION

- Drug D expects to dock at site because it has right configuration and be metabolized (Drug D is a substrate)
- Drug C blocks the site (lower Ki) and doesn’t allow D to be metabolized -> Drug D enters the system circulation “unmetabolized”
- Drug C is a CYP-inhibitor
- DDI occurs almost immediately and it doesn’t matter which drug is added first

CYP Inhibition

CYP1A2 substrate

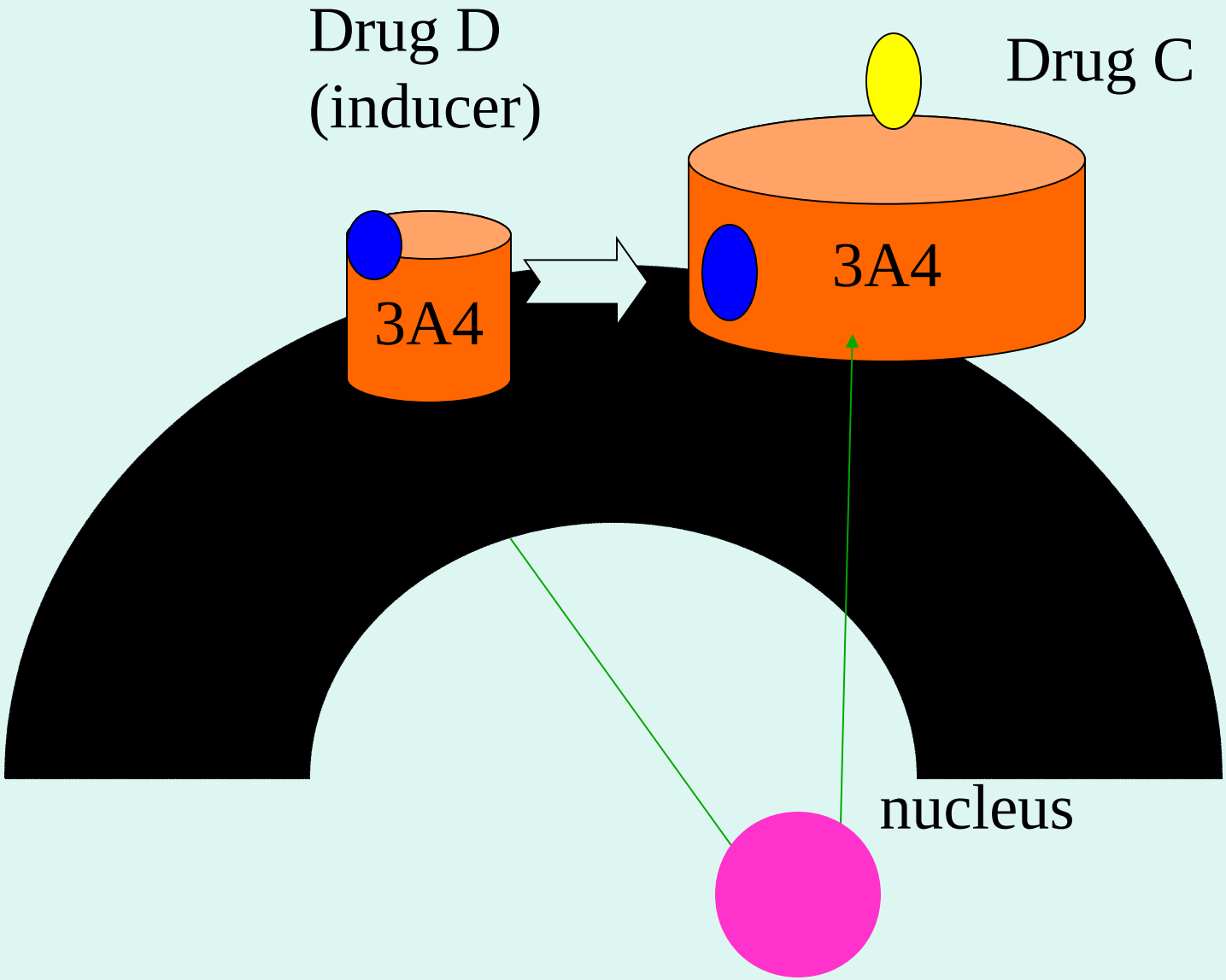
CYP1A2 inhibitor



CYP1A2

How do CYP-based DDIs occur? INDUCTION

- Drug C is a substrate of CYP 3A4 and Drug D is an inducer
- Drug D docks at CYP 3A4 and sends a message to nucleus to make more CYP protein (put more “men” on the line)-takes a few days
- After new CYP protein is made-- Drug C will be “chewed up” more extensively so that less of it will enter the systemic circulation
- Matters which drug is first-DDI will take some time to develop if drug D added second, but a DDI will occur immediately if it already present for several days



Drug D sends message to nucleus to make more CYP protein---Induction of 3A4-

> lower concentration of Drug C

Pharmacokinetic v. Pharmacodynamic DDIs

- DDIs of these types are pharmacokinetic as well as those the “body does to the drug”: (gi, plasma, liver, kidney)
- DDIs at the receptor level-and beyond “what the drug does to the body” (e.g., serotonin syndrome)

CYP Genetics

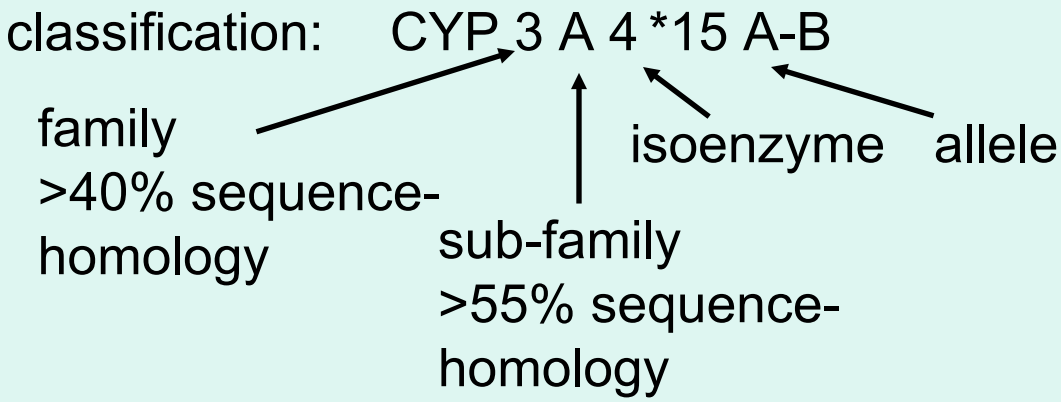
- If the CYP docking site is “faulty” so that Drug C cant dock--> higher systemic plasma concentrations (Slow metabolizer)
- If there are multiple copies of the docking site (more men on line), Drug C is metabolized more efficiently--> lower plasma concentration (Ultra-rapid metabolizer)

Naming-Cytochrome P450s

- CY (first 2 letters)---P (protein) and 450--- (from the observation in the lab of the wave length of absorption when CO infused)
- Nomenclature was invented to describe the relationship of CYPs to each other-- no clinical significance
- Amino acids of each CYP elucidated and a nomenclature based of how similar CYPs are to each other

Cytochrome P450 Naming

Cytochrome P450 Naming



Naming UGTs

- Same system as CYPs
- Family- arabic number
- Subfamily- letter
- Gene-arabic number (e.g., UGT1A1, UGT1A4, UGT2B7)
- Allele * number (UGT1A1 *2A)

What CYPs important in drug metabolism

- CYP1A2-chromosome 15
- CYP2C9-chromosome 10**
- CYP2C19-chromosome 10**
- CYP2D6- chromosome 22**
- CYP2E1-chromosome 10
- CYP3A (4/5/7)-chromosome 7

** most genetic information

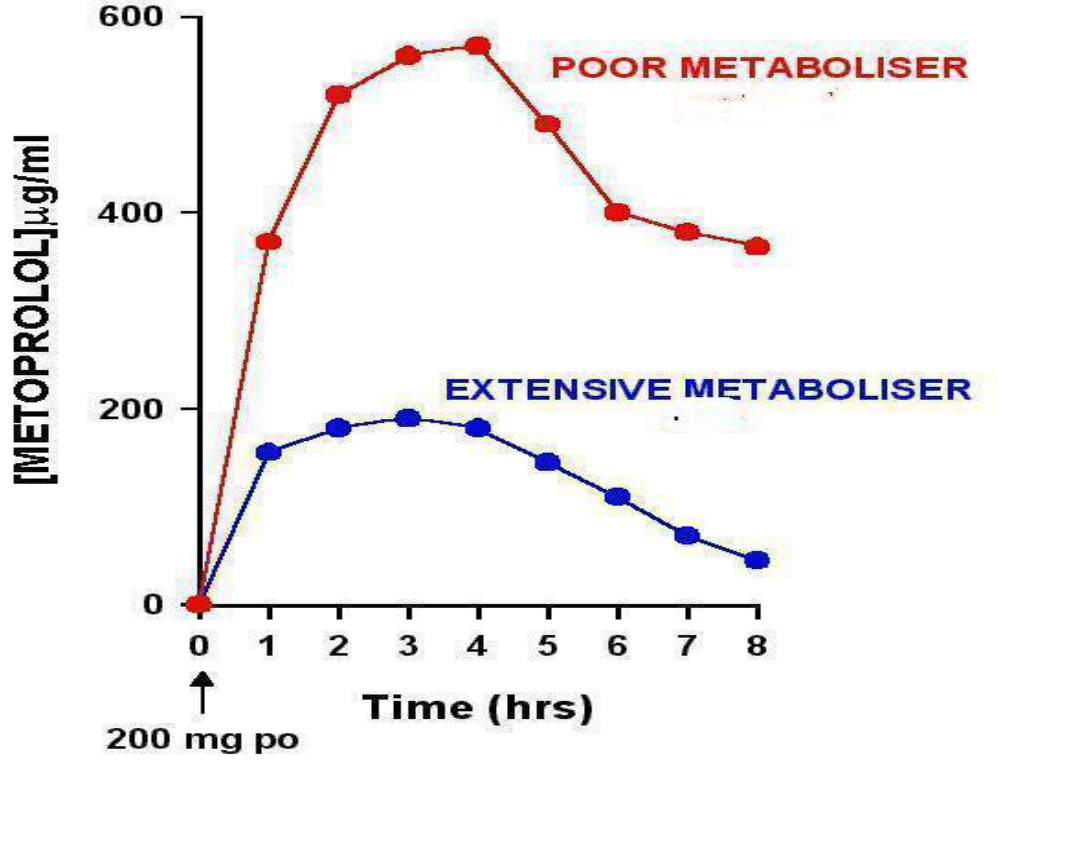
CYP2D6 genetic polymorphisms as example

- Norm is the “extensive metabolizer”
- Gene inactivation “poor metabolizer”
- 7-10% of whites and African American and 1% Asian
- Variant of gene (Intermediate PM)-20% of Asians--> low level of functional CYP- “not quite poor metabolizer”
- Ultrarapid Metabolizers- 20% of Saudis/Ethiopians- survival value of detoxification of plants during starvation
- CYP2C9 and 19 have genetic poor metabolizer variants that are clinically important

CYP 2D6 Polymorphisms CYP alleles: 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

Clinical Implications of CYP2D6 variants:



UGT-Genetics

- UGTs differ from CYPs in that both endogenous and exogenous compounds are conjugated
- UGT1A1 is the site for bilirubin conjugation
- Partial absence (30%) Gilberts syndrome with fluctuating hyperbilirubinemia and increased systemic levels of substrates
- Total absence Crieglar-Najjar syndrome

Lets look at the CYP Chart

- Organized according to a particular CYP with substrate, inducer and inhibitor arranged vertically
- Some drugs metabolized by a single CYP (desipramine, quinidine) and others by multiple pathways (promiscuious, sertraline)
- Some classes of drugs mostly under one CYP (NSAIDs) and others not (SSRIs)
- Drug don’t have to be a substrate of a CYP to either induce or inhibit it (e.g., quinidine)
- Use this table to predict DDIs

Vignette

- 14 year old girl with depression has had a good response to fluvoxamine. She has asthma and is placed on theophylline. Within a day, she develops headache, nausea and palpitations.

- Look at CYP chart under CYP1A2. Theophylline is a substrate and fluvoxamine and inhibitor. Example of drug added to inhibitor and theophylline toxicity develops
- If the inhibitor had been added to the substrate, toxicity would have developed just as quickly.

Vignette on CYP3A

- Patient is on carbamazepine and levels are steady at 6 ?meq/mL. He has a sore throat and he is given erythromycin by his internist. Within a day, he develops signs of CBZ toxicity ataxia, dizziness and vomitting.

Answer

- Erythromycin is a potent CYP3A4 inhibitor and increases the levels of carbamzepine.
- Doesn’t matter which is added first-> same result

Vignette

- A 41 year old woman is on warfarin after a thrombophlebitis. She is quite depressed. What antidepressant would be safest to use?

Warfarin story

- Narrow therapeutic range-INR
- Warfarin is a racemic mixture
- S-warfarin is more biologically active, contributes about 70% of activity-substrate of 2C9
- Look at the CYP Chart for anti-depressants that are inhibitors/inducers of CYP2C9
- Actually R-warfarin is a substrate of 2C19, 1A2 and 3A, but it can inhibit 2C9

Vignette

- 18 year old woman is on oral contraceptives. She develops grand mal seizures. What anti-seizure medications should not be used? Any herbs?
- Example of an inducer added to a drug
- Example of an inhibitor added to a drug

Vignette

- 18 year old abusing alcohol for 1 year stops drinking. On day 1, he takes 6 tablets of acetaminophen. 36 hours later he comes to the ER with hepatitis.

Acetaminophen Toxicity - News

A BITTER PILL FOR WINNER IN TYLENOL-DAMAGE SUIT
$5 MILLION FAILS TO SETTLE VA. MAN'S CONCERNS

Washington Post (Wednesday, January 17, 1996 ; Page D01)

Six weeks ago, Antonio Benedi walked out of his lawyer's office with a check for more than $5 million, courtesy of a federal jury that found the makers of Tylenol liable for destroying his liver. When he reached his Springfield home, he placed the check on the night table next to his bed. For two days, he stared at it, trying to figure out how his entire life had been reduced to a handwritten number on a piece of paper.

FDA ORDERS ALCOHOL-PAINKILLER WARNINGS

Washington Post (Thursday, October 22, 1998 ; Page A11□)

If three alcoholic drinks a day is your routine, the government wants you to check with your doctor before reaching for that bottle of painkiller.

Answer to vignette

- Acetaminophen is metabolized by a number of different pathways, and one pathway is to N-acetyl-p-amino benzoquinone (NAPQI) which is a hepatic toxin via CYP2E1. Chronic ingestion of alcohol induces CYP2E1. Since CYP2E1 is induced, more acetaminophen goes to the toxic metabolite.
- This was not an overdose attempt!

Example of a drug added to an inducer-no delay

Vignette

- After a suicide attempt a 28 year old 2-pack a day smoker is admitted to the hospital (which prohibits smoking). He is begun on fluvoxamine to 200 mg daily, but appears to have no response. He is discharged after 4 days. He does not resume smoking. He gradually develops symptoms of headache, sleepiness and nausea.

Example of an Inducer removed from a drug-happens over time (de-induction)

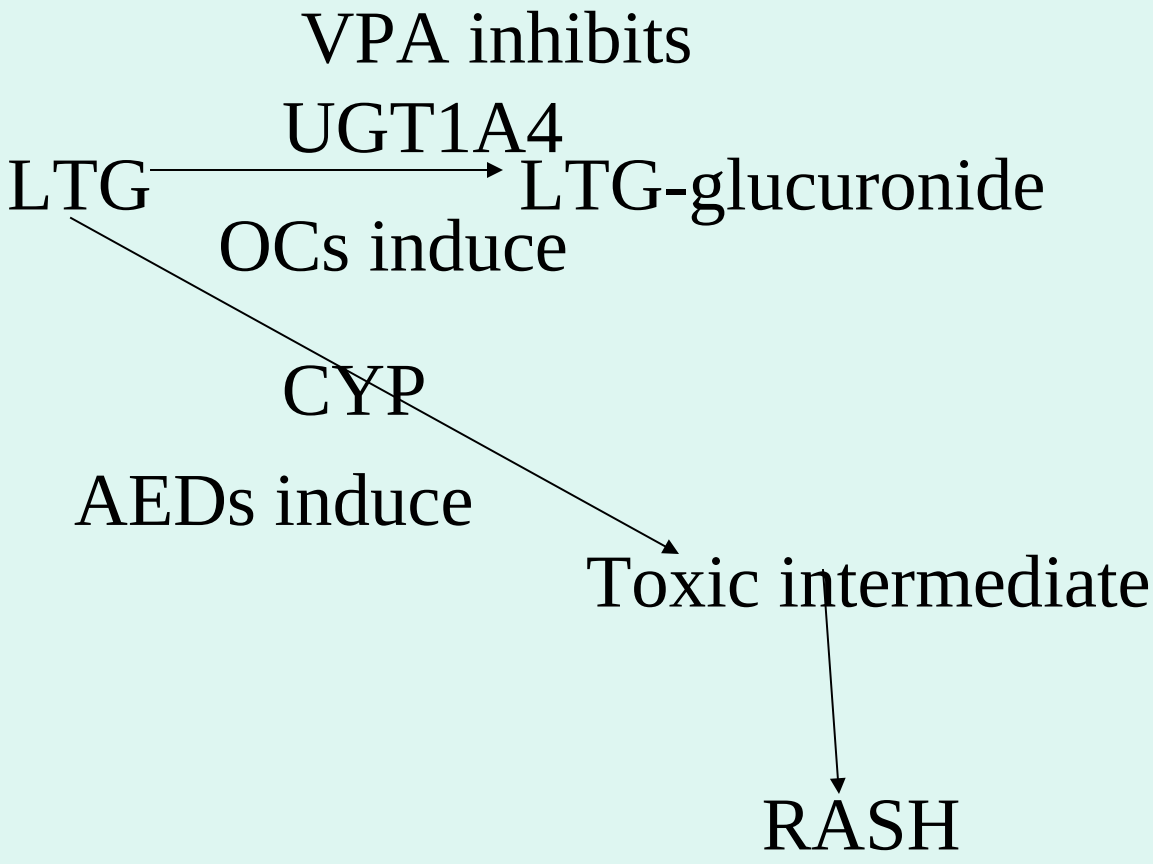
Vignette

- 26 year old is on paroxetine. After fracturing his leg, he is given hydrocodone. He experiences NO analgesia.

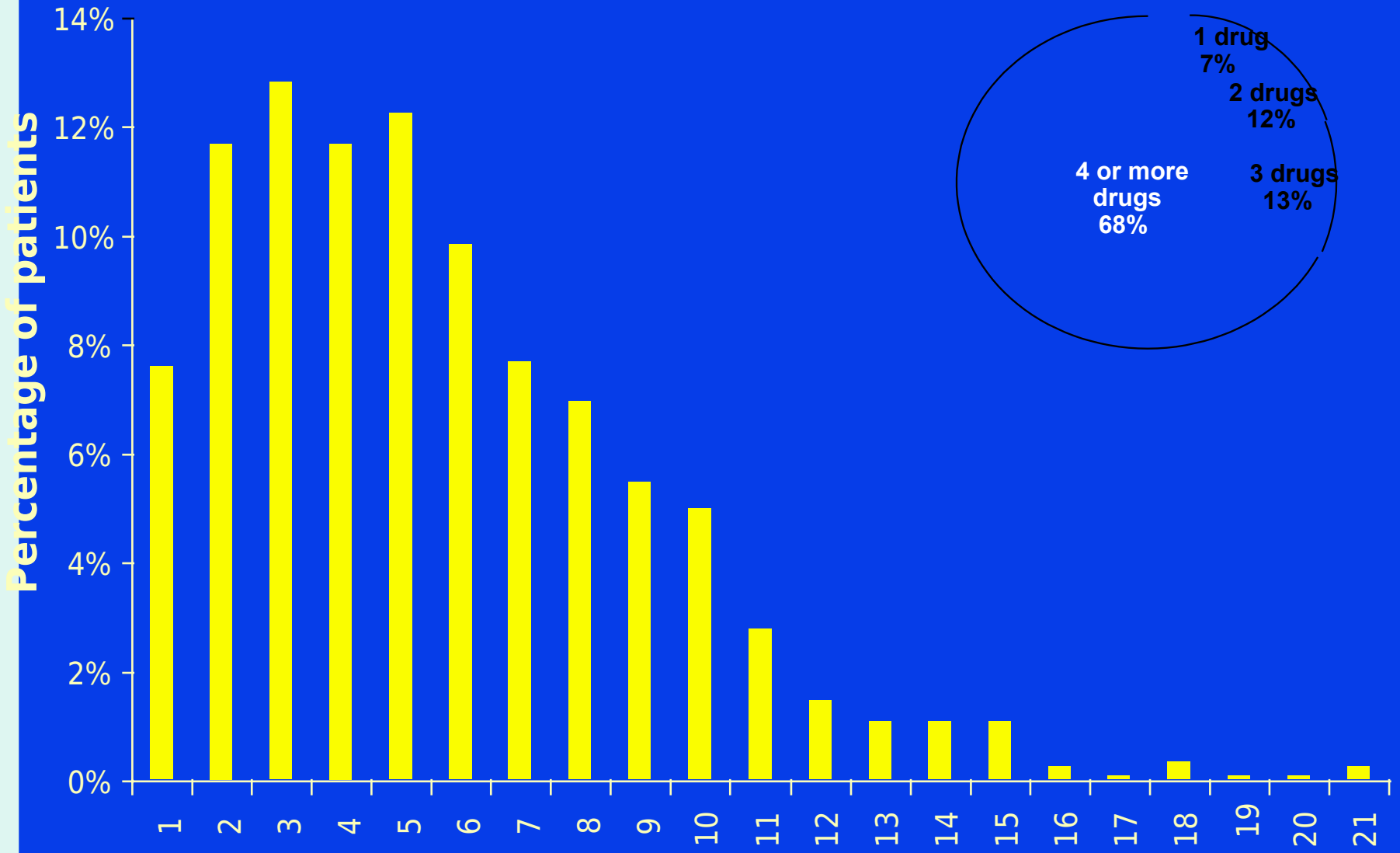
Example of a pro-drug (metabolized by CYPs) added to an inhibitor-look at CYP2D6 on CYP chart.

Some other CYP pro-drugs: tamoxifene, mestranol and desogestrel containing OCs

UGTs-Lamotrigine Metabolism



VA Medical Center (in- and outpatients) (n=1076)



Shad MU, et al. Clin Pharmacol Ther. 65:183, 1999. Abstract PIII-25

Nobody can remember all of the DDIs

- Make sure you know ALL of the over-the-counter, herbals etc a patient is taking
- Ask- is there anything I shouldn’t give you?
- Narrow your personal formulary and learn the CYP pathways of the drugs you use commonly
- Use the CYP Chart
- Know the real clinical effects of the DDI (eg. paroxetine and DMI-400% v sertraline and DMI-25%)
- Know if the substrate has a wide or narrow therapeutic index

On a patient visit

Be particularly vigilant if any drug or herbal or OTC has:

- a narrow therapeutic index (VPA, theophylline, CBZ)
- causes serious side effects (prolonged QTc, rhabdomyolitis, lower seizure threshold, pregnancy)
- is a potent inhibitor or inducer (older anticonvulsants, many HIV drugs)
- has a single metabolic pathway

Red Flag Drugs

- Older AEDs: carbamazepine, phenobarbital, phenytoin
- Cimetidine
- Cyclosporine
- HIV drugs
- Ketoconazole, Itraconazole , Fluconazole
- Nefazodone
- Macrolide antibiotics – Erythromycin
- Oral contraceptives
- Quinolones; ciprofloxacin, enoxacin
- Rifampin
- Statins
- St. John’s wort
- Theophylline
- Warfarin
- Grapefruit juice (lots of)

Remember the “DDI Patterns”

- Focus in on the last med change if there are any new symptoms
- Watch for new symptoms that occur in a time frame consistent with DDI “patterns”
- Add drug to inhibitor, inhibitor to drug and drug to inducer and removal of inhibitor---> immediate effect
- Inducer to drug and removal of inducer--> delayed effect