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

J R Oesterheld, MD

Question 1

Most drug-drug interactions are caused by

A-transporter-transporter interactions

B-UGT-UGT interactions

C-UGT-P450 ctyochrome interactions

D-P450 cytochrome-p450 cytochrome interactions

E-All of the above

Question 2

- If a patient is currently on oral contraceptives, what mood stabilizer can be added without concern for a possible drug interaction?

A-carbamazepine

B-valproate

C-oxcarbazepine

D-lamotrigine

E-lithium

Question 3

- Patient is on carbamazepine for bipolar disorder. He develops an infection and is started on erythromycin by his family doctor. What happens to the levels of carbamazepine?
- A-stays the same
- B-increases
- C-decreases

Question 4

- Patient is on cyclobenzaprine and is depressed. What drug will increase its levels?
- A-fluvoxamine
- B-bupropion
- C-venlafaxine
- D-sertraline
- E-None of the above

Question 5

- Pt is on paroxetine for anxiety. They are in an automobile accident and receive codeine for pain. What is the likely outcome?
- A-no analgesia because codeine is a prodrug
- B-extra analgesia because codeine is a prodrug
- C- no analgesia because codeine levels are increased
- D- no analgesia because paroxetine is an inducer of CYP2D6
- E- extra analgesia because paroxetine is an inhibitor of CYP3A4

Major Teaching Points

- CYP induction and inhibition responsible for lion share of drug interactions
- Can predict CYP-based drug interactions by knowing substrates, inhibitors, inducers
- Certain drugs are more likely to cause drug interactions

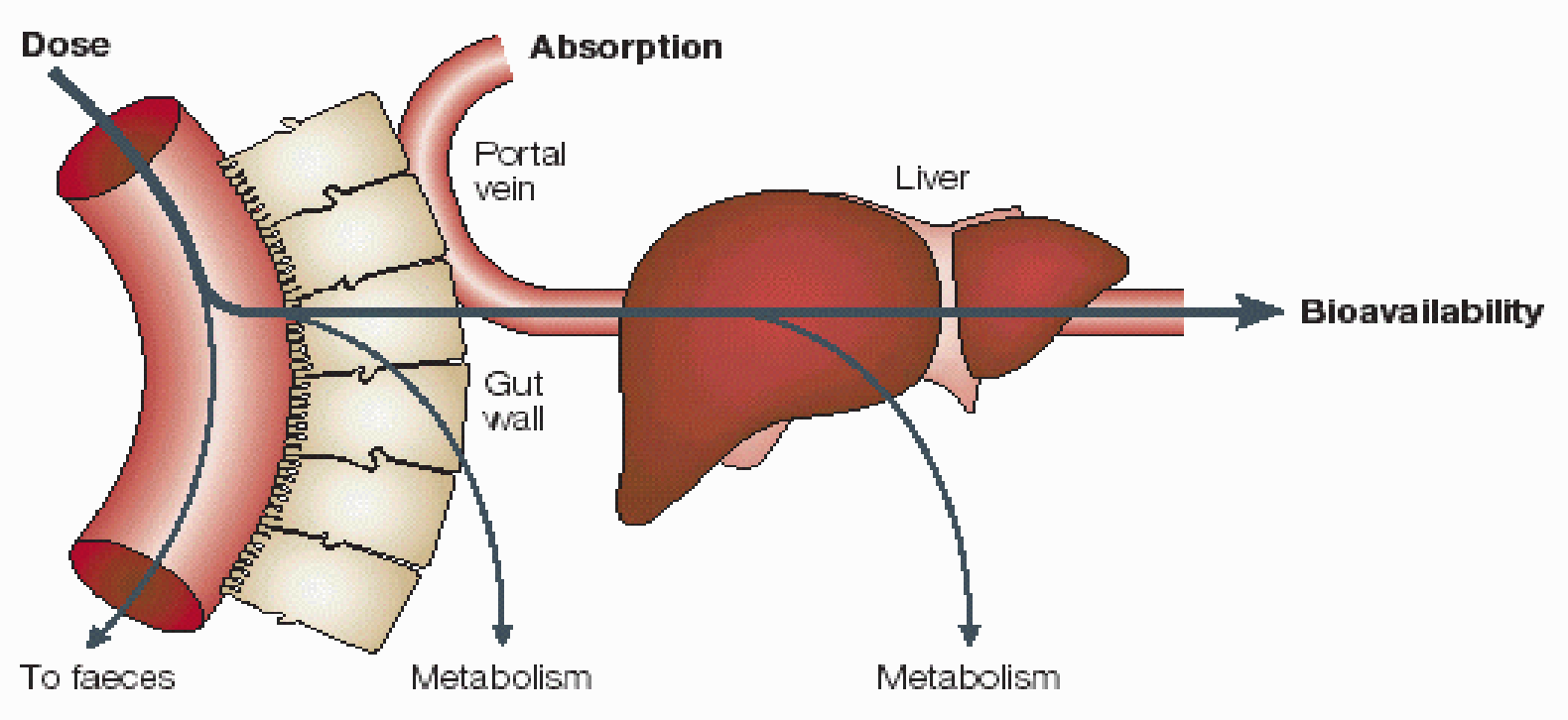
What will we do today?

- 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 factories 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

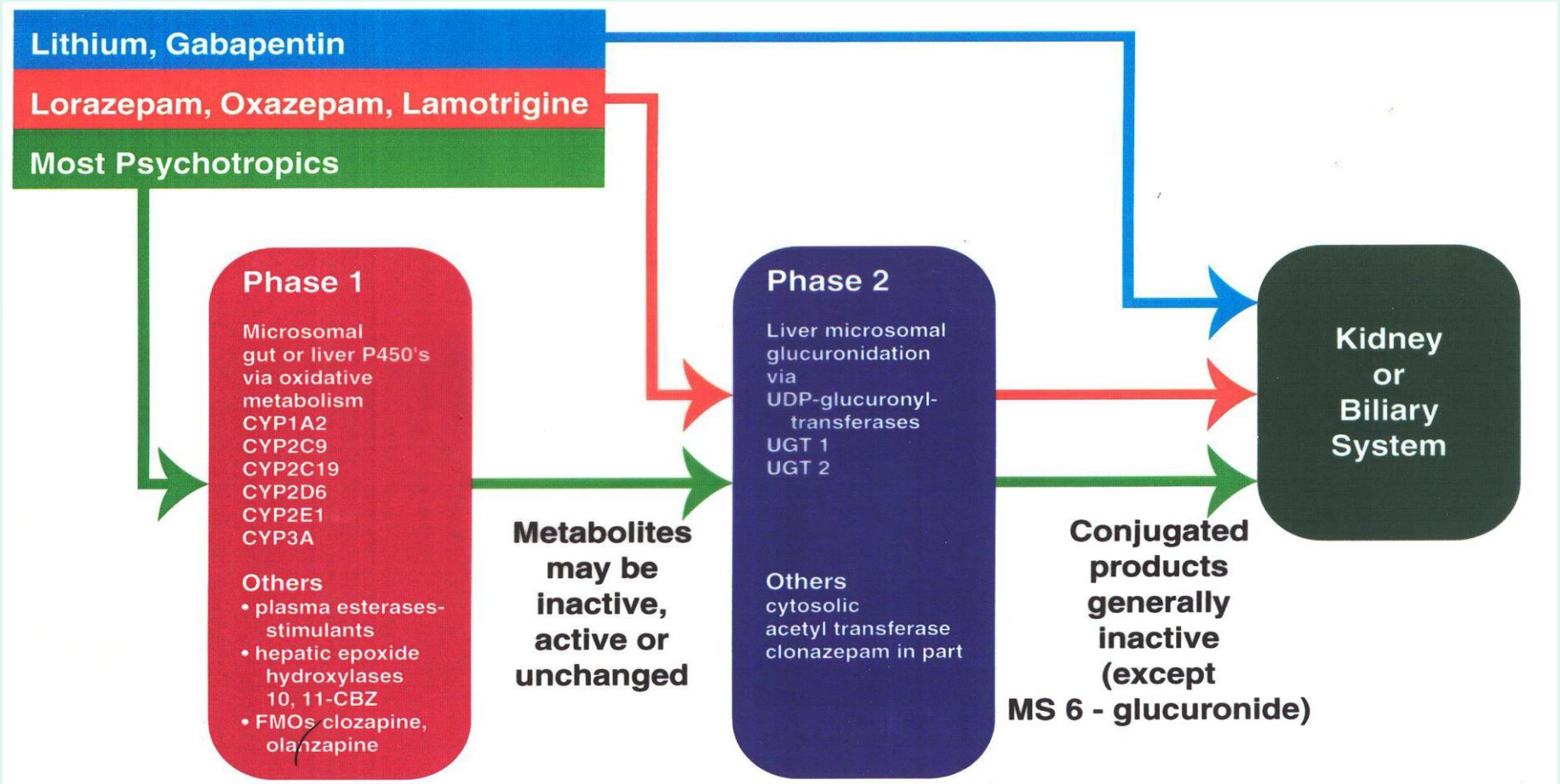


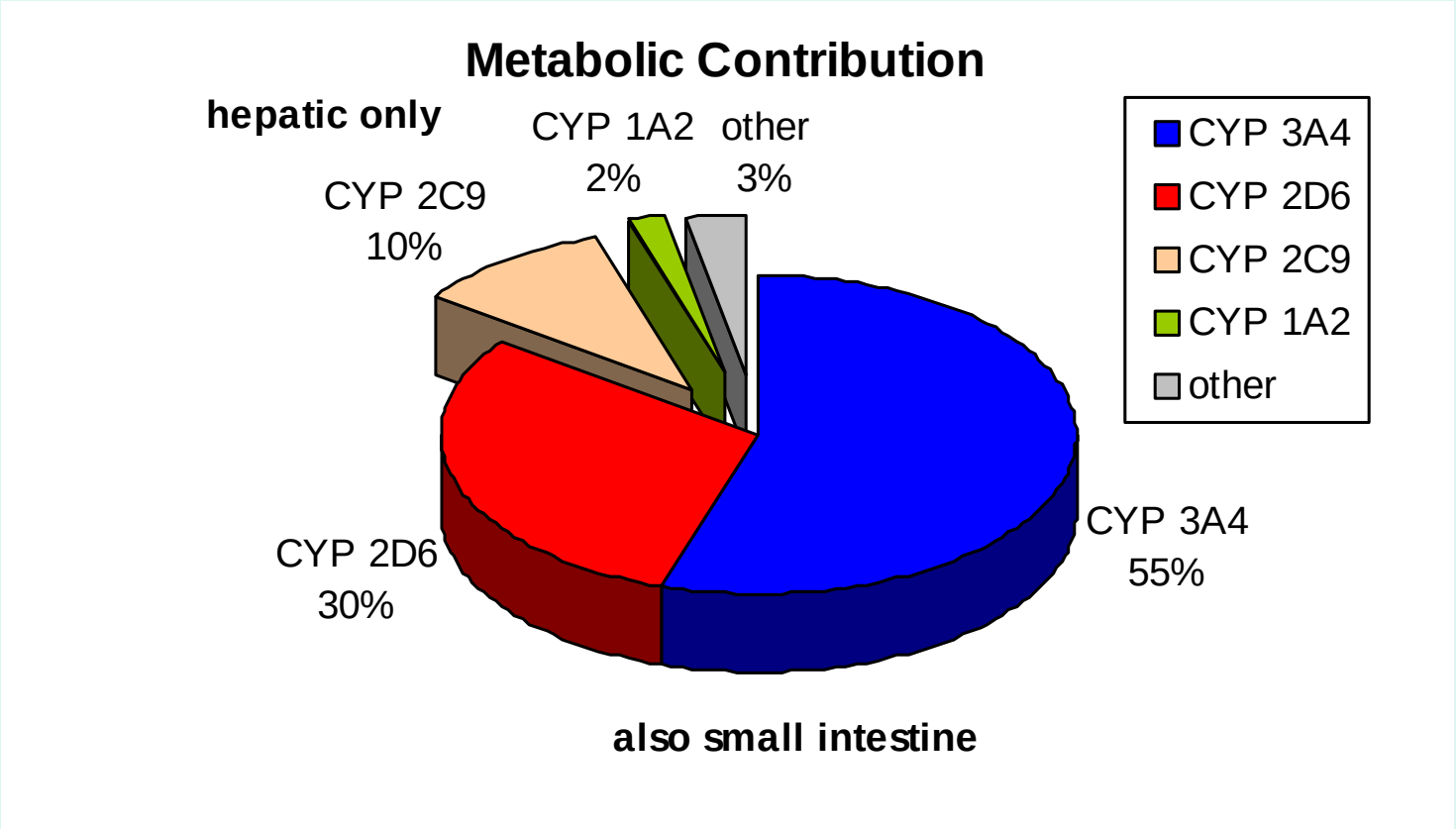
Figure 2. Phase 1 and Phase 2 Biotransformation

What are CYPs?

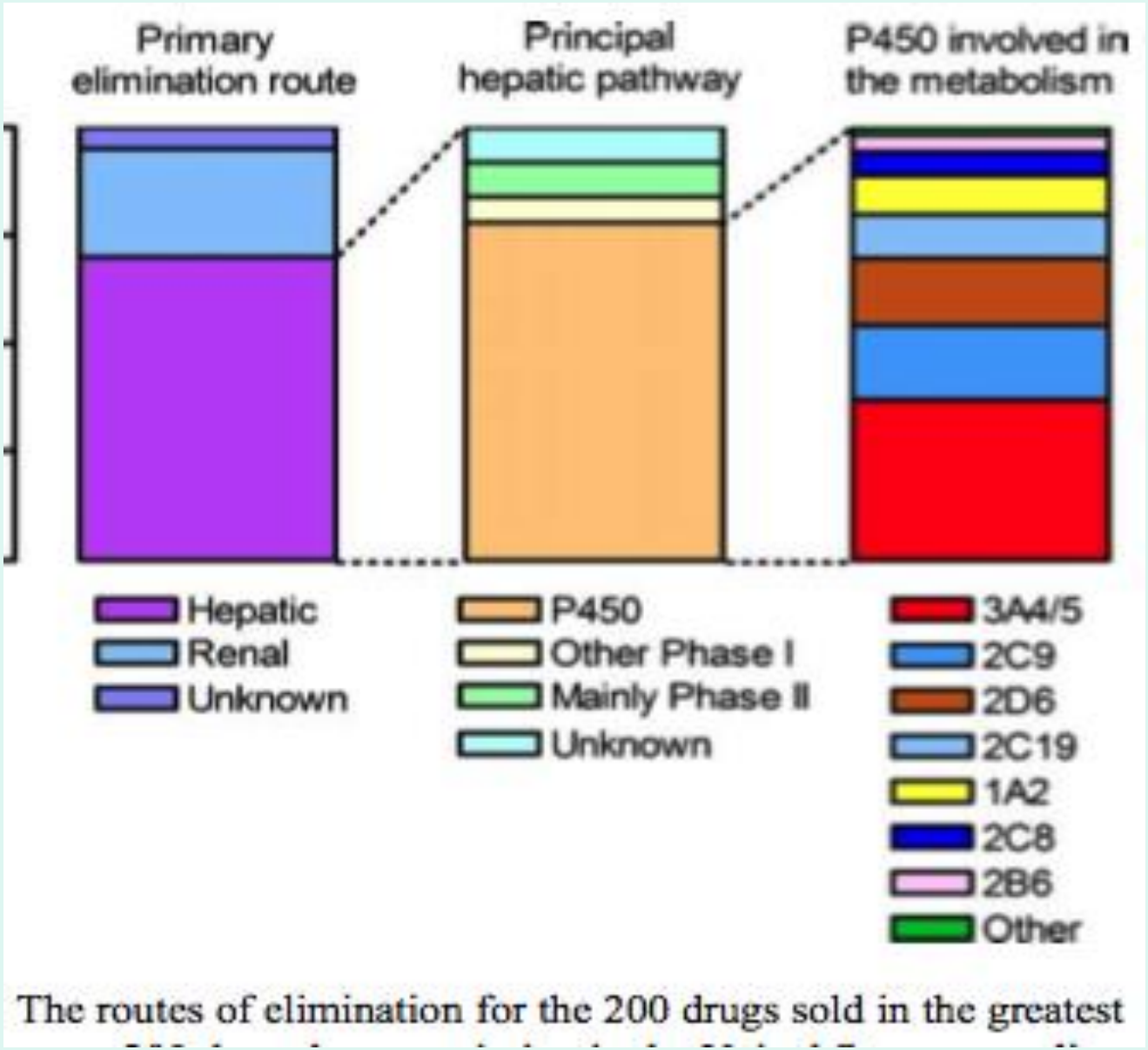
- Millions of years ago, plants developed toxins (so not to be eaten) and animal retaliated by developing metabolic factories to chew the toxins up safely
- Superfamily of heme-containing enzymes
- 2 kinds, some in mitochondria that chew up endogenous products (e.g. steroids) and those tp be discussed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

Cytochrome P450 enzymes

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

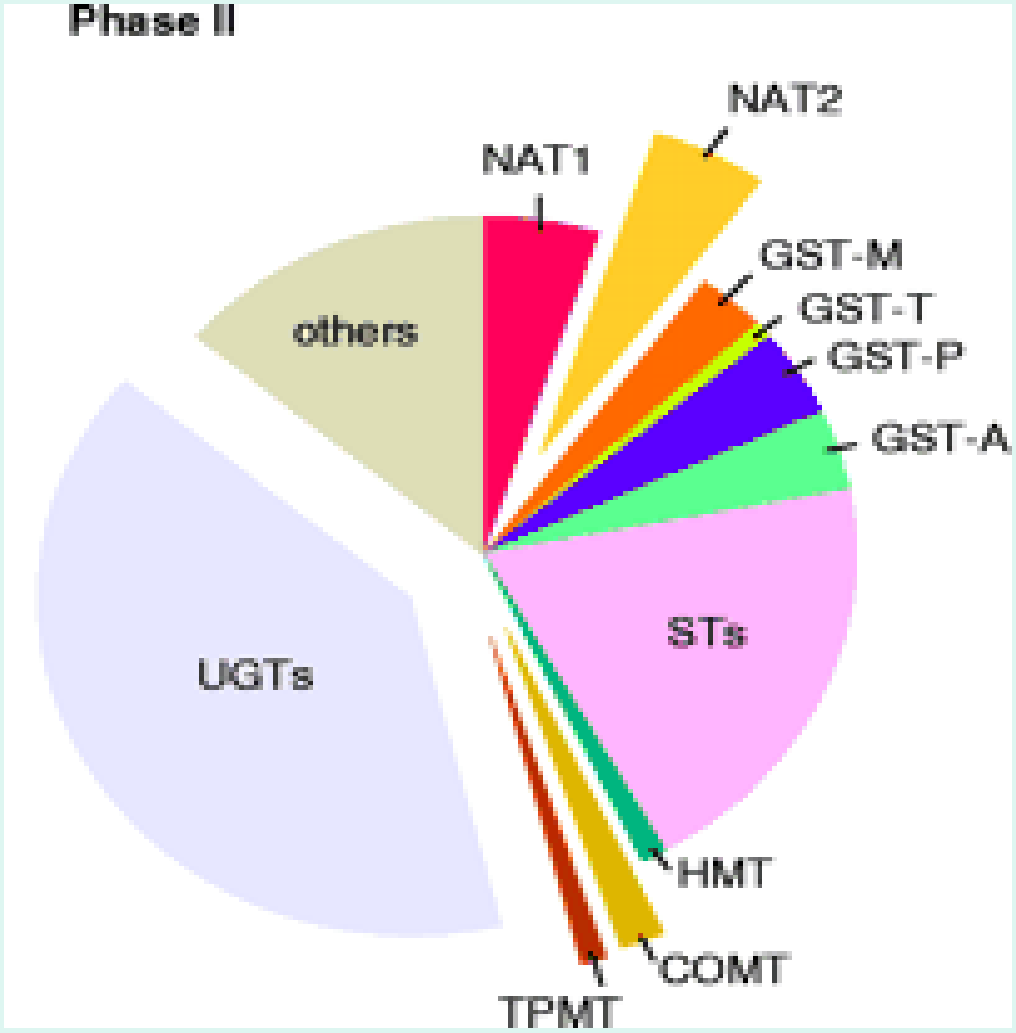


Zanger 2008



The routes of elimination for the 200 drugs sold in the greatest

Phase 2 transferases (conjugation)



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

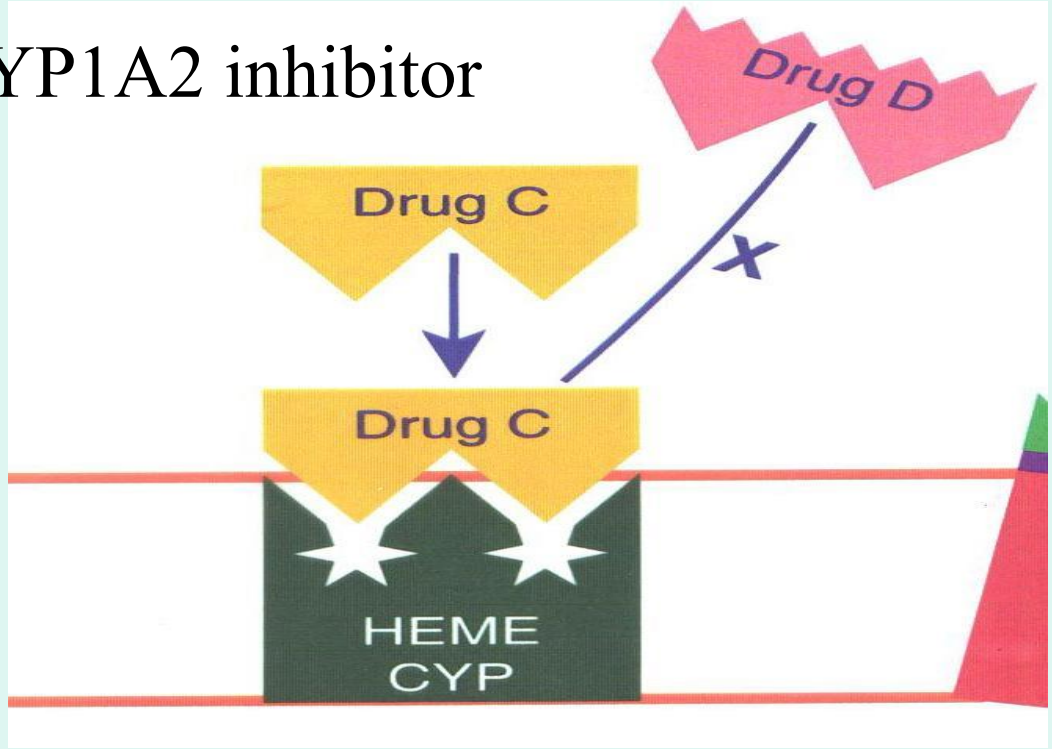
How do CYP-based DDIs occur? INHIBITION

- 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

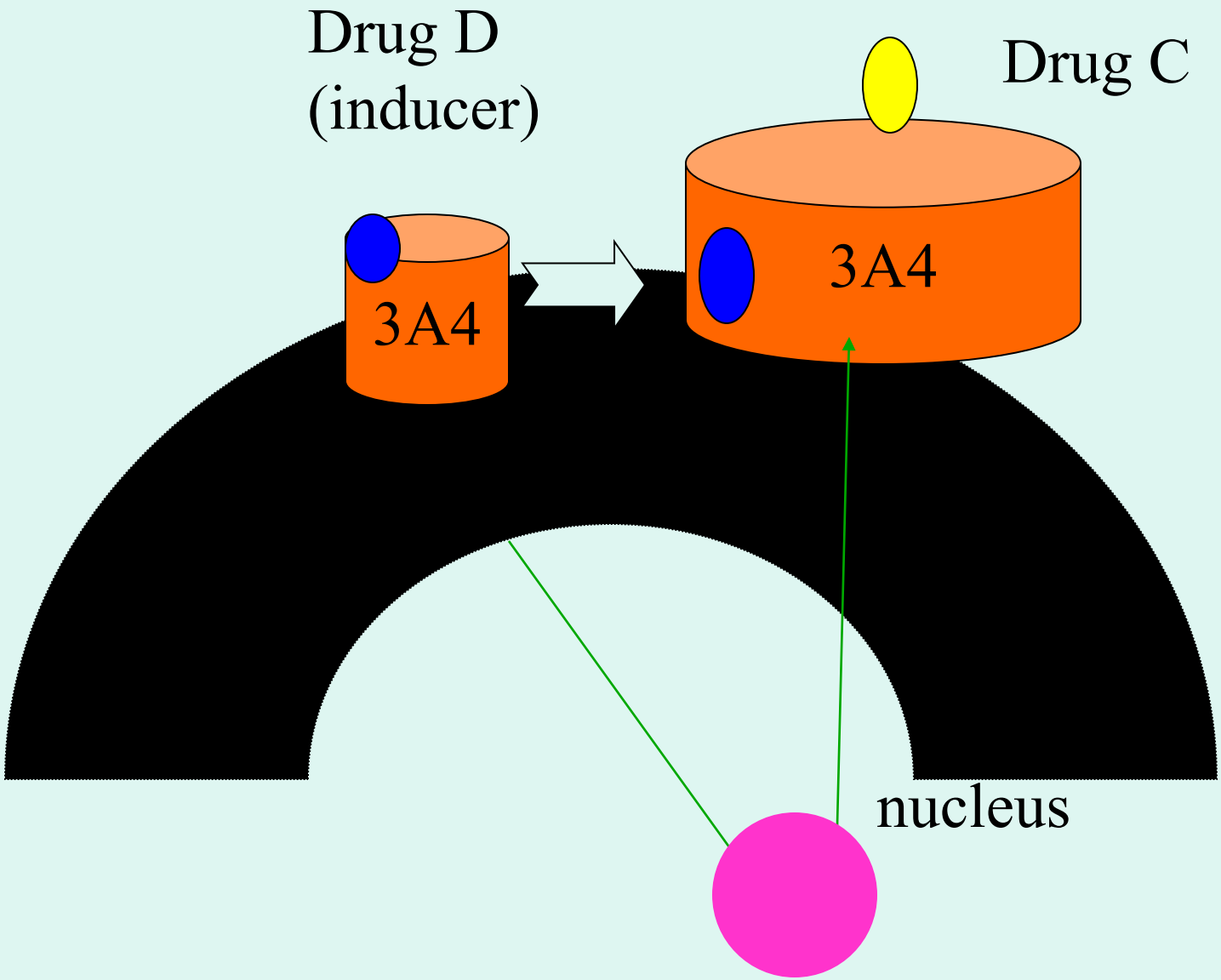
CYP1A2 inhibitor



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

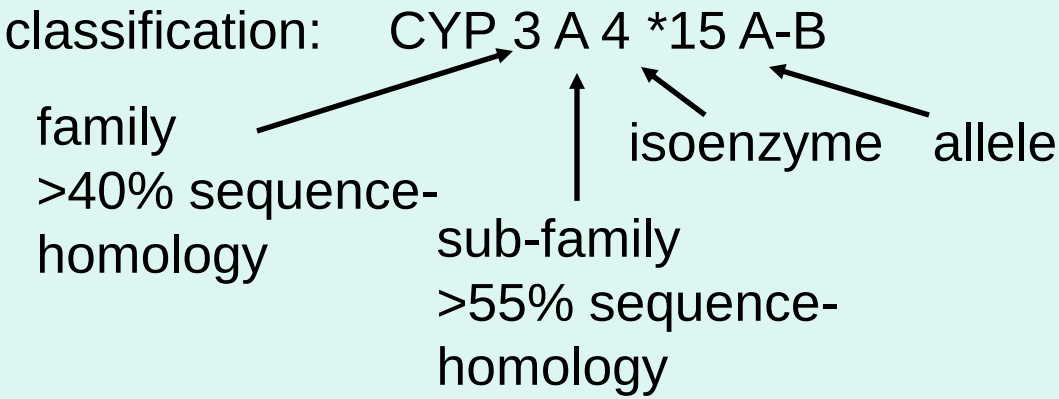
- If the CYP docking site is “faulty” so that Drug C cant dock--> higher systemic plasma concentrations (Slow metabolizer)
- If there are multiple copies of the docking site (more men on line), Drug C is metabolized more efficiently--> lower plasma concentration (Ultra-rapid metabolizer)

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
- CYP2B6- chromosome 19
- CYP2C9-chromosome 10
- CYP2C19-chromosome 10
- CYP2D6- chromosome 22
- CYP2E1-chromosome 10
- CYP3A (4/5/7)-chromosome 7-isozxymes

CYP2D6 Potential Phenotypes

- *Poor Metabolizers*
  - lack functional enzyme.
- *Intermediate Metabolizers*
  - heterozygous for one functional and one deficient allele
  - have two partially defective alleles that cause reduced metabolism
- *Extensive Metabolizers*
  - two normal alleles
  - often majority of population
  - "normal metabolizers
- *Ultra-Rapid Metabolizers*
  - duplicated or multiduplicated functional CYP2D6 genes with extremely high metabolic capacity.

Genetic polymorphisms

- CYP2D6 poor metabolizer"-7-10% of whites and African American and 1% Asian *3,4,5 involved in major genetic polymorphism PM - 90 %
- CYP2D6 Ultraextensive Metabolizers- 20% of Saudis/Ethiopians- survival value of detoxification of plants during starvation
- CYP2C19 has genetic poor metabolizer variants that are clinically important: CYP2C19*2, *3 in 18-23% Asians, 2-5% Caucasians
- CYP2 C9*2 and*3 present in about 7% of Caucasians and much less frequent in Asians or African-Americans

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:

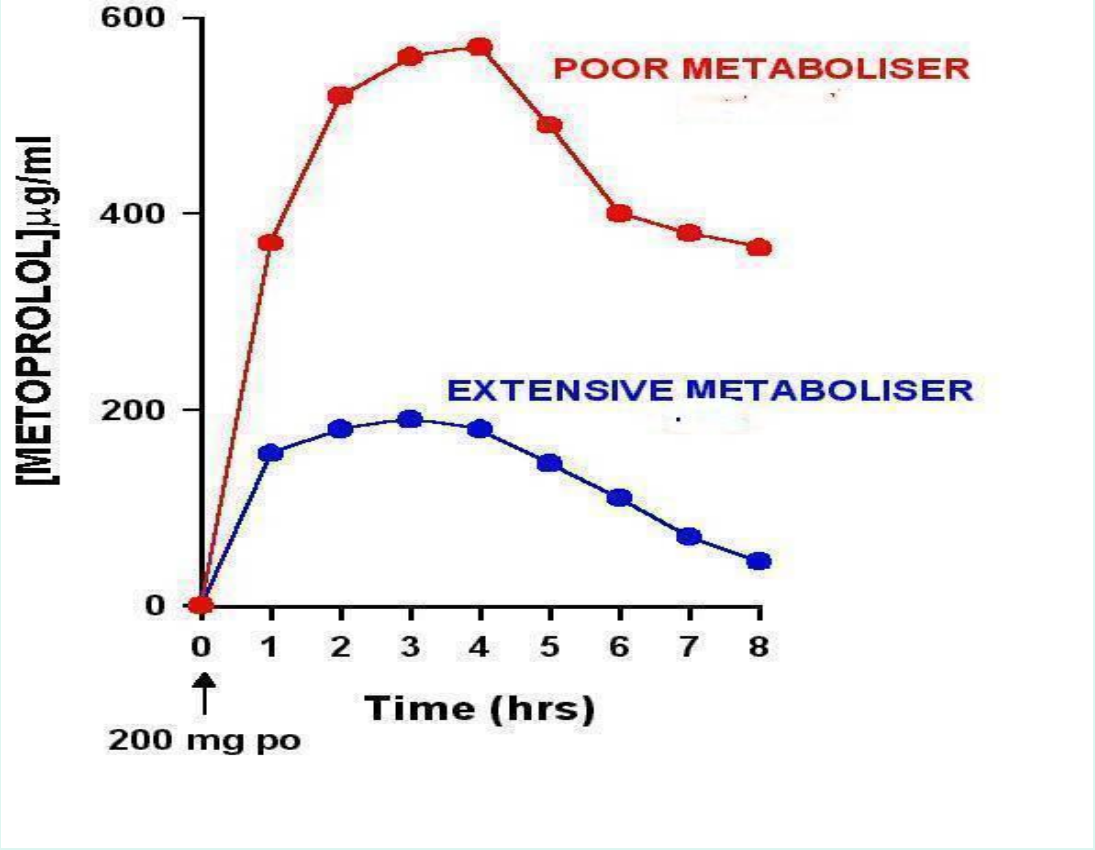


Table 3. Incidence of the cytochrome P450 CYP2D6 enzyme phenotypes among different ethnic populations.

Population	PM phenotype (%)	Diminished activity of IMs (%)	UM phenotype (%)	Reference
White		1–2		[1]
American	7.7		4.3	[20, 4
British	8.9			[26]
Polish	8.3			[73]
Swiss	10			[25]
Danish			0.8	[22]
German	7.7		0.8	[49]
Swedish			1	[50]
Spanish			10	[23]
Turkish	1.5		8.7	
Croatian	3.0		4.0	[74]
African				
African-American	1.9–7.3		4.9	[20, 39–42]
Nigerian	0–8.1			[35, 36]
Ghanaian	6.0			[37]
Ethiopian	1.8		29	[21]
South African	19			[38]
Asian		51		[1]
Japanese	0			[29]
Chinese	<1.0		0.9	[28, 75]
Thai	1.2			[27]
Indian	1.8–4.8			[30–33]
Saudi Arabian	1–2	3–9	21.0	[1, 51, 76]
Hispanic				
Colombian	6.6		1.7	[47]
Mexican	3.2			[46]
Panamanian (Amerindian)	2.2–4.4			[45]
Nicaraguan	3.6			[48]

Abbreviations: IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

From Bernard et al 2006

Nuclear Receptors in Enzyme Induction of Drug Metabolizing Enzymes

Receptor	CYPs induced	Inducers	Other enzymes induced
Aryl hydrocarbon (Ah/XRE*)	CYP1A1, CYP1A2, CYP1B1	Cigarette smoking, barbecued food and omeprazole	Glutathione transferases (GST) Glucuronlytransferases (UGT)
Constitutive androstane (CAR)	CYP2B6, CYP2A6, CYP3A†	Phenobarbital, amobarbital, secobarbital butobarbitone, heptobarbitone, glutethimide, promethazine	Epoxide hydrase, GST, UGT Cytochrome P450 reductase
Pregnane X (PXR)	CYP3A4, CYP3A5, CYP3A43†, CYPs2A†, CYPs2C†, CYP2E1†	Rifampicin, carbamazepine, dexamethasone, phenylbutazone, phenytoin, sulfadimidine, sulfinpyrazone; phenobarbital†, St John's Wort	Cytochrome P450 UGT†
Peroxisome proliferator-activated (PPAR)	CYP4A	Fibrate anti-hyperlipidaemics	Cytochrome P450 reductase
TR	CYP reductase	Thyroid hormone (T3)	
Unknown	2E1	Ethanol and chloral hydrate, isoniazid	

*XRE = xenobiotic responsive element (nuclear binding site) for the Ah receptor

†These items are suspected but not yet proven

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 (“promiscuous are not inhibited”, 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 CYP1A2

- 28 year old man with spinal injury has had a good response to tizanidine (Zanaflex). He develops a UTI and ciprofloxacin is added. Within a day, he develops increasing sedation and some hypotension.

CYP1A2

- Look at CYP chart under CYP1A2. Tizandine is a substrate and Cipro an inhibitor. Example of drug added to inhibitor and tizanidine adverse effects develops
- If the inhibitor had been added to the substrate, adverse would have developed just as quickly.
- What to do?

Vignette CYP1A2

- 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)
think of other possible sequences of adding or substracting an inducer

Vignette CYP2B6

- Patient placed on Ticlid post coronary stent. Is it a good idea to recommend use of bupropion to reduce smoking with it? If there is a DDI, when will it occur?

Answer

- Cmax of bupropion will be increased 38%
- Keep dosage of bupropion low and monitor fore adverse effects (e.g., agitation, dizziness, tremor, drowsiness, nausea, tachycardia.

Vignette CYP2C9

- A 41 year old woman is on warfarin after a thrombophlebitis. She is quite depressed. What antidepressant would you start her on?

Vignette CYP2C19

- A 50 year old accountant has been taking 5 mg diazepam tid for 15 years along with 5-10 mg in addition during times of increased stress (pre April 15the season). After symptoms of indigestion and heartburn in late March, internist prescribed omeprazole 20 mg/day. An period of intense calm ensues without need for the usual increase in diazepam.

Vignette CYP2D6

- A 40 year old women with depression has failed 4 SSRIs and venlafaxine. She is placed on amitriptyline (AMI) 200 mg/day with a blood level of 197 ng/ml (AMI + nortripytline). Bupropion XL 300 mg is added and women gradually develops lethargy and blurry vision.

Vignette CYP2D6

46 year old woman has breast cancer and is on tamoxifen. She is depressed. What will happen if fluoxetine is added?

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

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

Vignette on CYP3A4

- 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 vomiting. The crafty among you will also note that in time, 7-10 days, the levels of erythromycin (a substrate of CYP3A4) will start to decline since carbamazepine is also an inducer of CYP3A4.

Answer

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

Vignette on CYP3A4

- 18 year old woman is on oral contraceptives. She develops grand mal seizures. What anti-seizure medications should not be used and why? Any herbs? Memorize the CYP3A4 inducers.

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

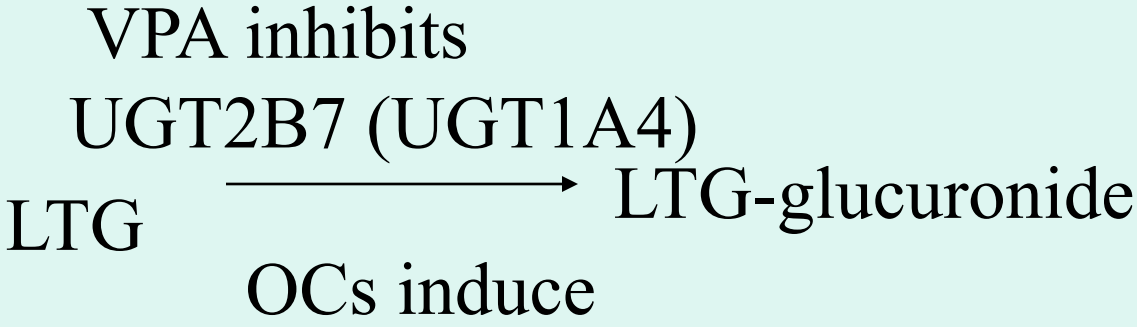
Washington Post (Thursday, October 22, 1998 ; Page A11□)

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!

UGTs-Lamotrigine Metabolism



Levels of Lamotrigine reduced

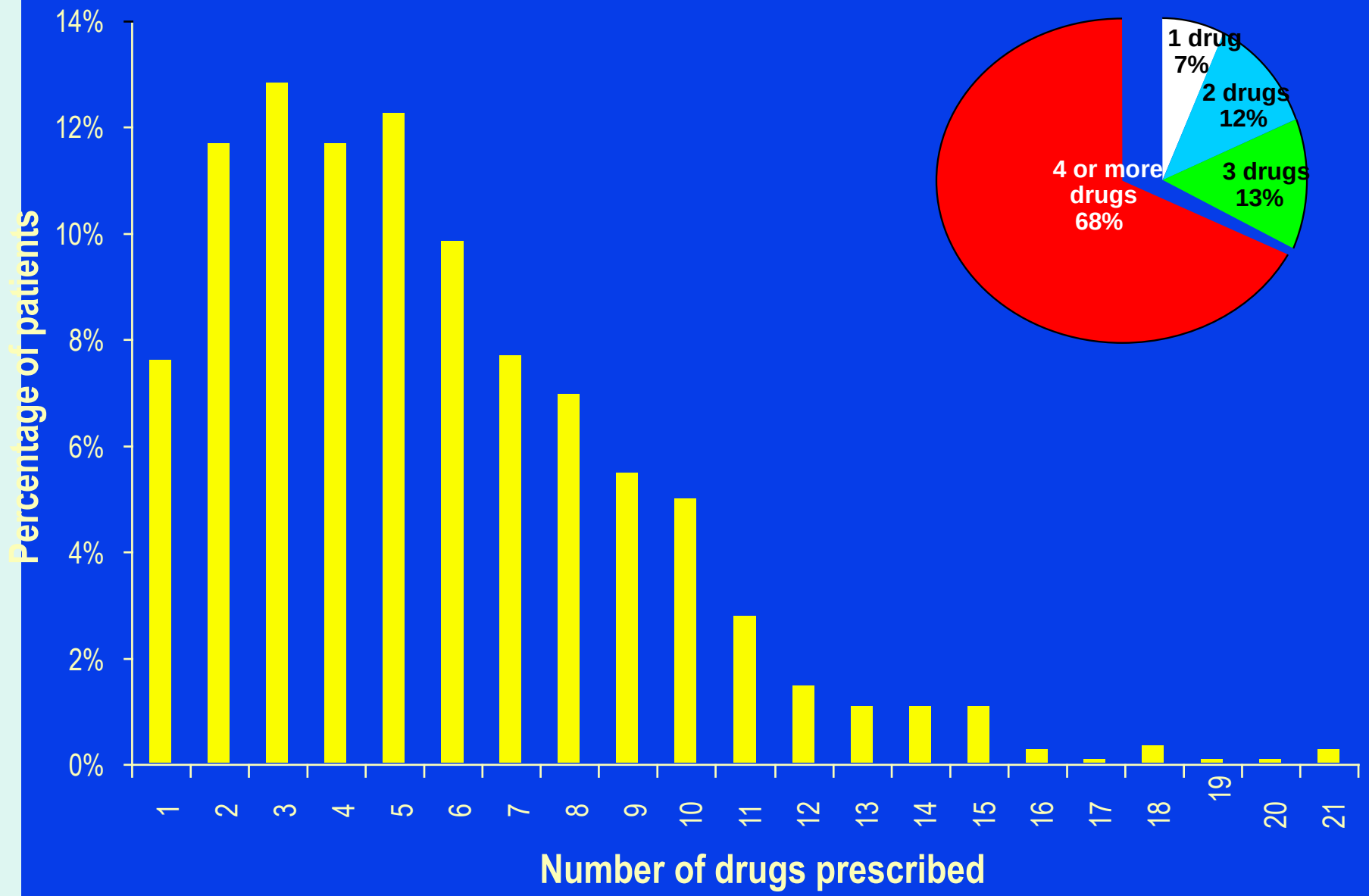
Also true of valproic acid

If patients on OCs and these drugs, there will be fluctuating levels if traditional week-free OCs used

Strategies when using OCs and lamotrigine or valproic

- Can substitute progestin only contraceptive since it does not induce UGTs
- Can keep patient on OCs that supply constant EE dosing (Seasonale and others)
- For lamotrigine, reduce dosing 25% during week-free traditional OC treatment

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
- Is a pro-drug

Red Flag Drugs-know which CYP they are substrates, inhibitors or inducers

- Older AEDs: carbamazepine, phenobarbital, phenytoin
- Amiodarone
- Cyclosporine
- HIV drugs
- Ketoconazole, Itraconazole , Fluconazole
- Nefazodone
- Macrolide antibiotics – clarithromycin and others
- 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

Question 1

Most drug-drug interactions are caused by

A-transporter-transporter interactions

B-UGT-UGT interactions

C-UGT-P450 ctyochrome interactions

D-P450 cytochrome-p450 cytochrome interactions

E-All of the above

Answer D

Question 2

- If a patient is currently on oral contraceptives, what mood stabilizer can be added without concern for a possible drug interaction?

A-carbamazepine

B-valproate

C-oxcarbazepine

D-lamotrigine

E-lithium

Answer E

Question 3

- Patient is on carbamazepine for bipolar disorder. He develops an infection and is started on erythromycin by his family doctor. What happens to the levels of carbamazepine?
- A-stays the same
- B-increases
- C-decreases

Answer =B

Question 4

- Patient is on cyclobenzaprine and is depressed. What drug will increase its levels?
- A-fluvoxamine
- B-bupropion
- C-venlafaxine
- D-sertraline
- E-None of the above

Answer is fluvoxamine

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- Pt is on paroxetine for anxiety. They are in an automobile accident and receive codeine for pain. What is the likely outcome?
- A-no analgesia because codeine is a prodrug
- B-extra analgesia because codeine is a prodrug
- C- no analgesia because codeine levels are increased
- D- no analgesia because paroxetine is an inducer of CYP2D6
- E- extra analgesia because paroxetine is an inhibitor of CYP3A4

Answer =A