Drug-Drug Interactions (DDIs)101

The ASCP Model Curriculum for Psychopharmacology, 8th Edition 2014

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Disclosure Slide

Dr. Oesterheld is the content editor of YouScript, a drug interaction application and a stockholder in Genelex.com that markets the program

Dr. Osser has no relationships to disclose

Pre-Lecture Exam Question 1

Most drug-drug interactions are caused by

A-transporter-transporter interactions

B-UGT-UGT interactions

C-UGT-P450 cytochrome 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

Patient is on paroxetine for anxiety. He is in an automobile accident and receives 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

- Cytochrome P450 (CYP) enzyme induction and inhibition is responsible for the lion's share of drug interactions
- You can predict CYP-based drug interactions by knowing substrates, inhibitors, inducers
- Certain drugs are more likely to cause drug interactions

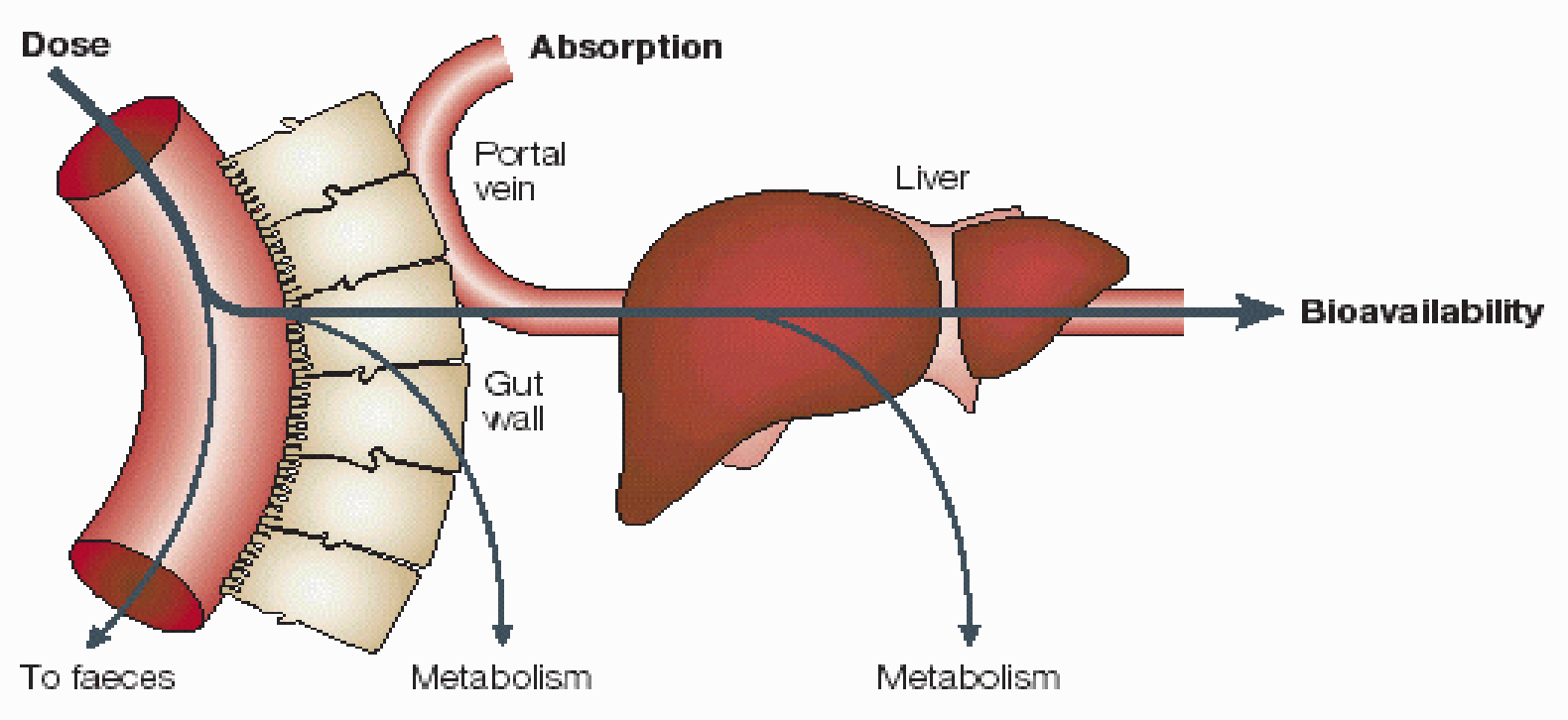
What will we do today?

- 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 UDP glucuronosyltransferase (UGT) -based DDIs e.g., those involving lamotrigine
- Mid-talk we will look at the 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 two 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 becomes more "water-loving" (so it can be excreted by the kidney or biliary systems) and becomes less toxic
- Phase 2 uses the handle to allow enzymes called transferases to hook up to Phase 1 products and further inactivate them and make them yet more hydrophilic: conjugation **with glucuronic acid, sulfate, acetic acid or an amino acid**

Examples of Phase 1 and Phase II

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

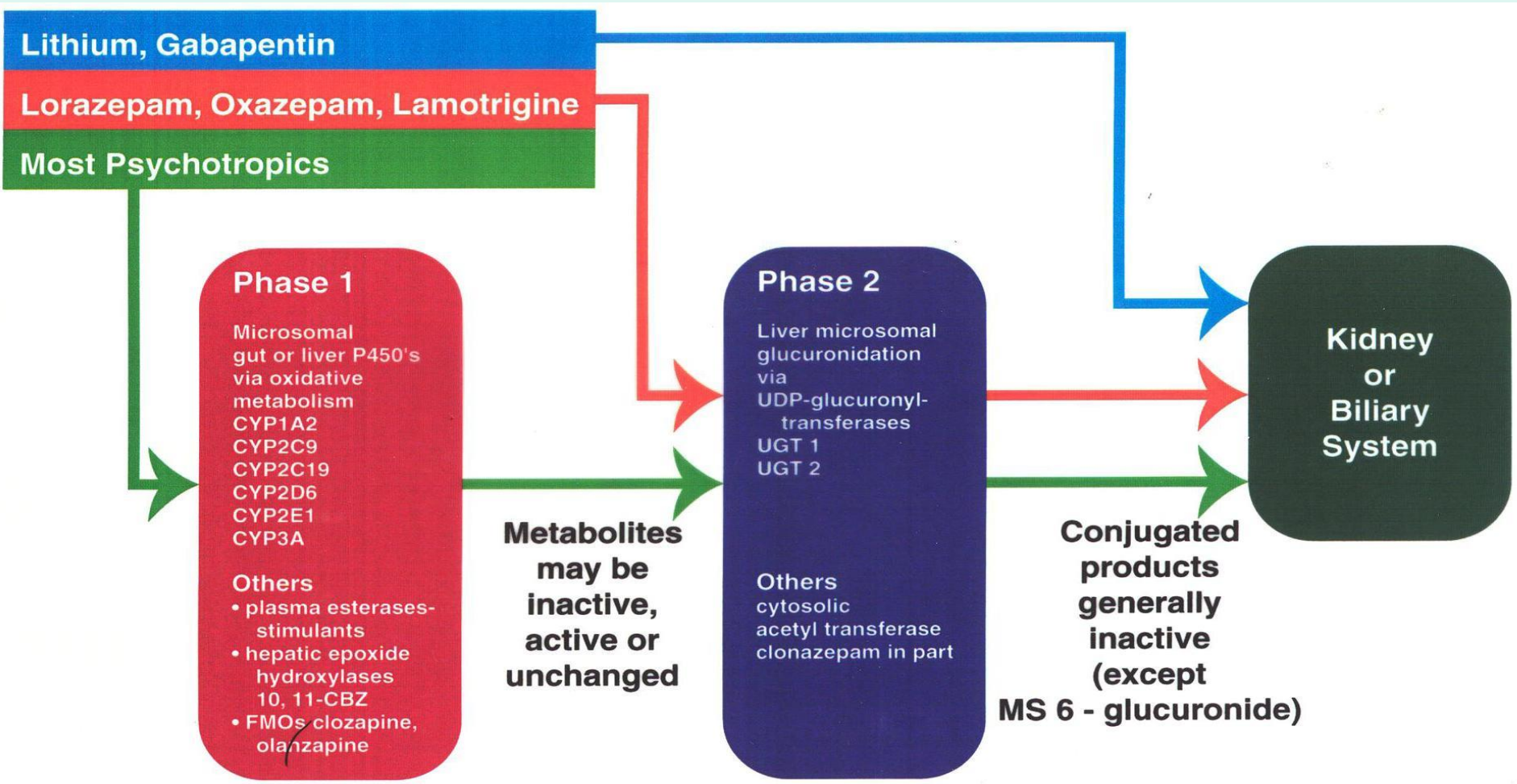


Figure 2. Phase 1 and Phase 2 Biotransformation

What are CYPs?

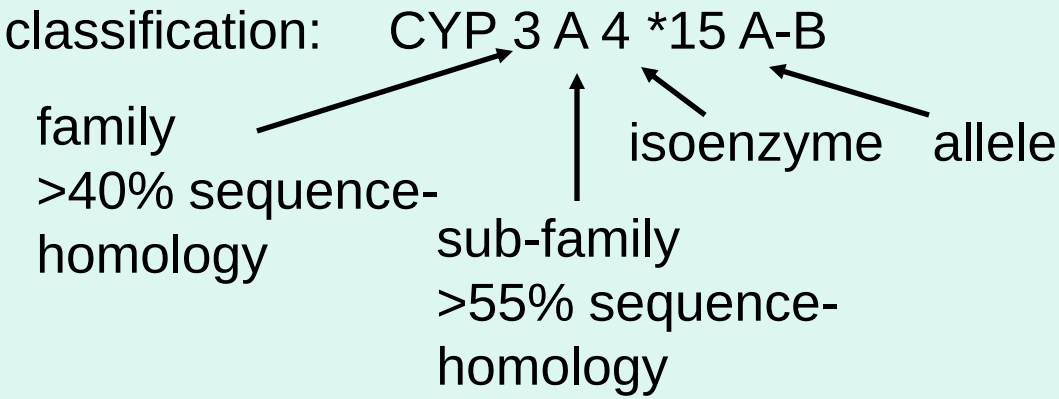
- Millions of years ago, plants developed toxins (so not to be eaten) and animals retaliated by developing metabolic factories to metabolize the toxins safely
- Superfamily of heme-containing enzymes
- 2 kinds, some in mitochondria that metabolize endogenous products (e.g., steroids) and those to be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

Naming Cytochrome P450s

- CY (CYtochrome)---P (protein) and 450---(from the observation in the lab of the wave length of light absorption when carbon monoxide is infused)
- Nomenclature was invented to describe the relationship of CYPs to each other – otherwise, no clinical significance
- Amino acid sequences of each CYP have been elucidated and the nomenclature is based partly on how similar CYPs are to each other

Cytochrome P450 Naming

Cytochrome P450 Naming

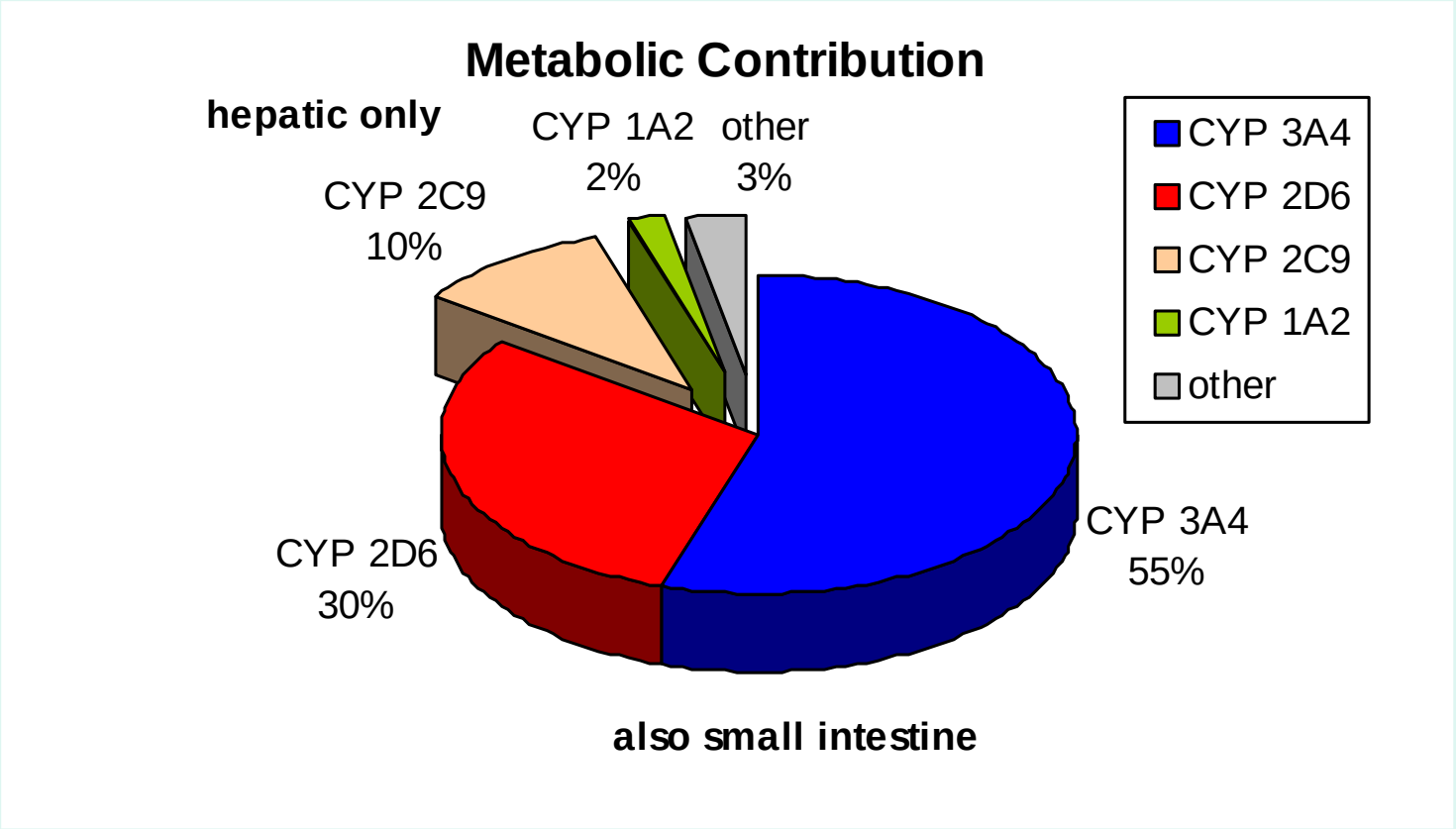


Naming UGTs

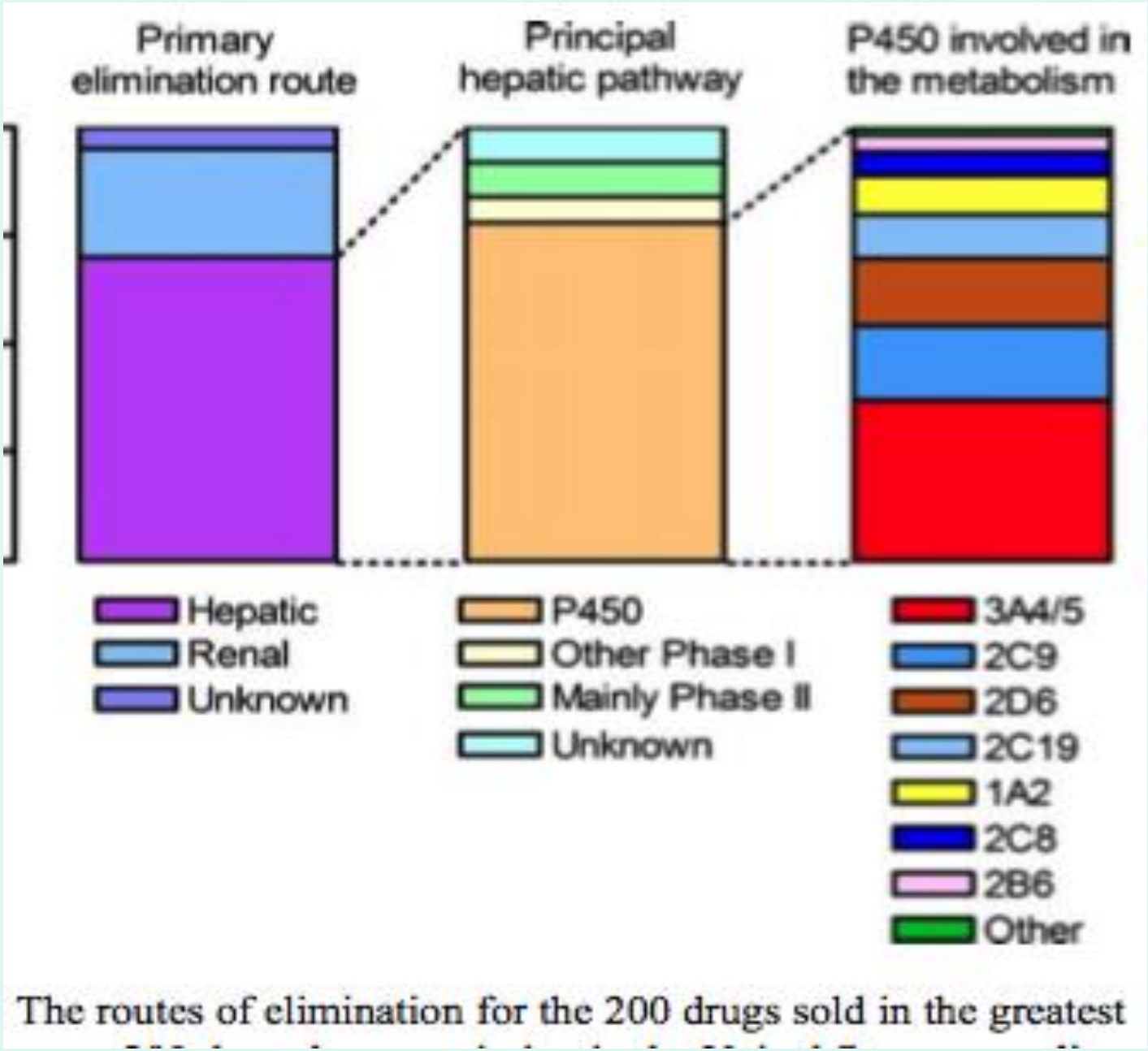
- Same system as CYPs
- Family - Arabic number
- Subfamily - letter
- Gene-Arabic number (e.g., UGT1A1, UGT1A4, UGT2B7)
- Allele * number (UGT1A1 *2A)

Cytochrome P450 enzyme frequency

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

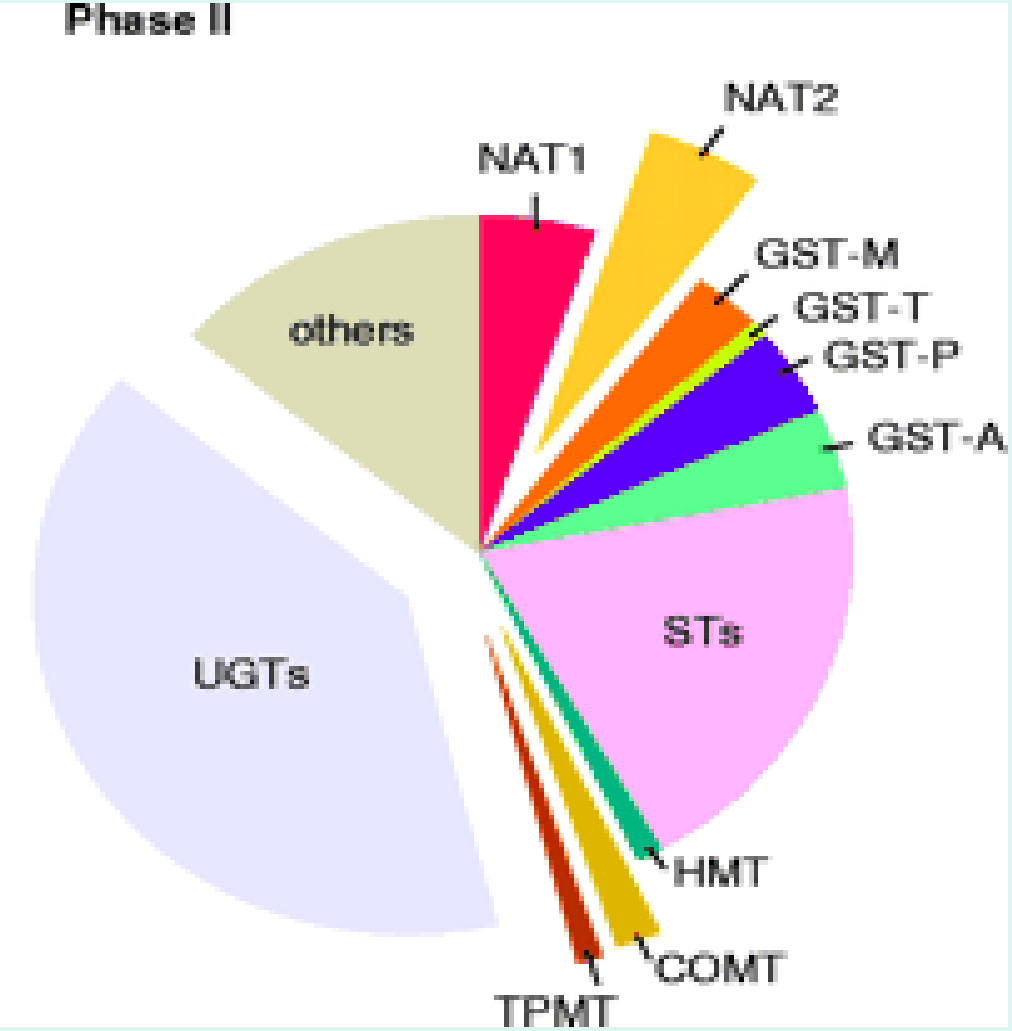


Zanger 2008



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.

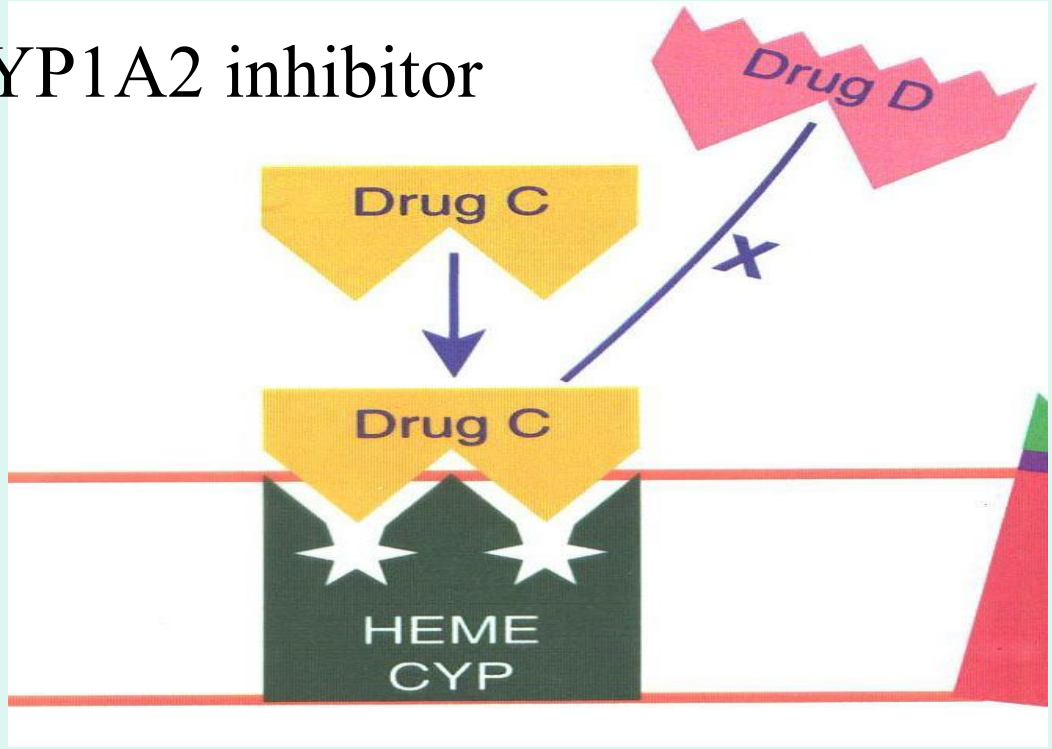
How do CYP-based DDIs occur? **INHIBITION** (Illustration on next slide)

- Drug D is the substrate. It has the right conformation to dock at the CYP site (1A2 in the illustration) and it gets metabolized there.
- Drug C is the CYP inhibitor. It blocks the site because it binds more strongly (lower coefficient of inhibition or Ki) and doesn't allow D to be metabolized -> Drug D enters the systemic circulation "unmetabolized"
- This DDI occurs almost immediately and it doesn't matter which drug is introduced first

CYP Inhibition

CYP1A2 substrate

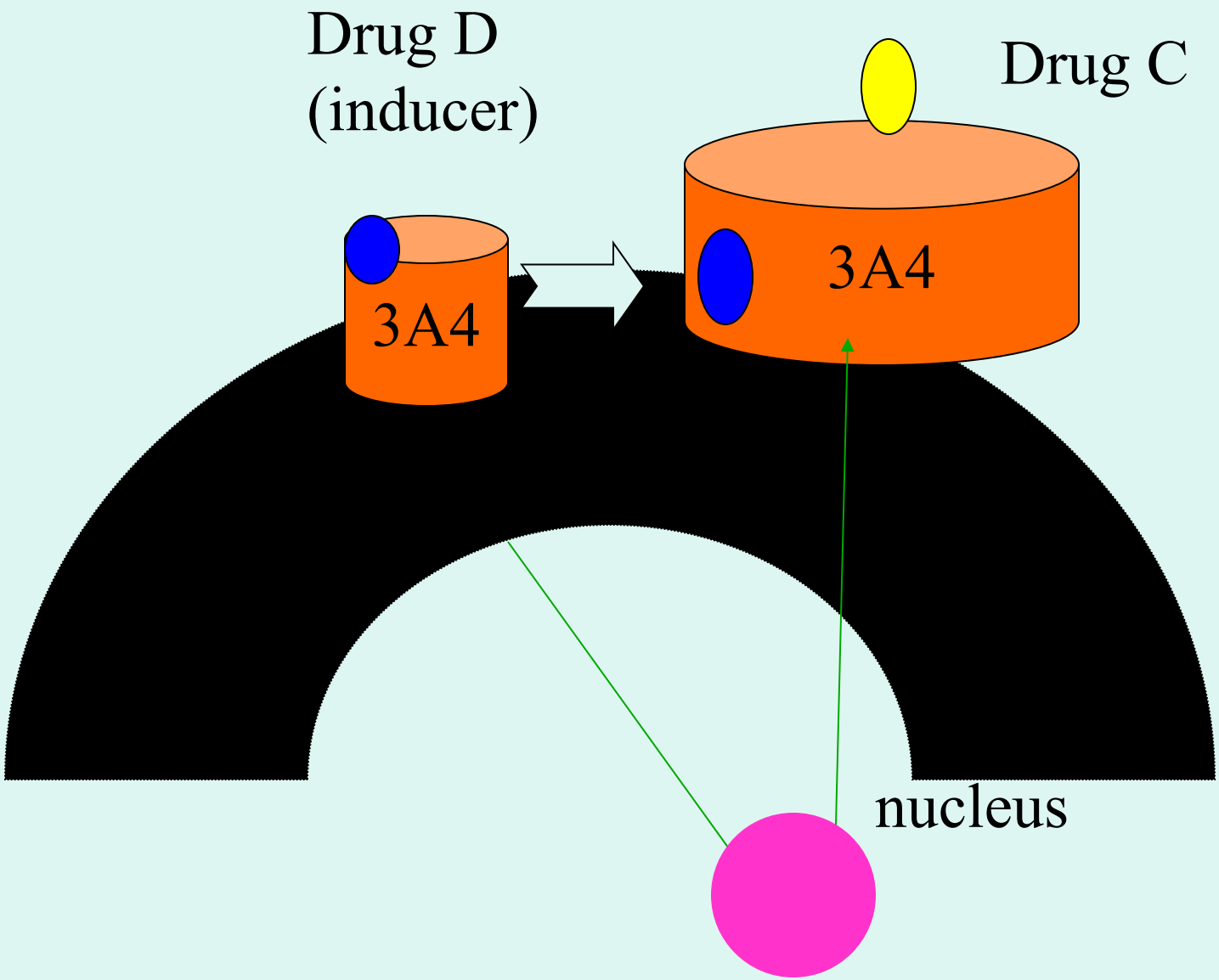
CYP1A2 inhibitor



CYP1A2

How do CYP-based DDIs occur?
INDUCTION
(see next slide for illustration)

- In this example, 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). This takes a few days
- After new CYP protein is made -- Drug C will be metabolized more extensively so that less of it will enter the systemic circulation
- It matters which drug is first. The DDI will take some time to develop if drug D added second, but a DDI will occur immediately if it is 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 vs. Pharmacodynamic DDIs

- DDIs of these types that are the focus of this lecture are termed "pharmacokinetic." They involve "things the body does to the drug." (occurs in GI track, plasma, liver, kidney)
- DDIs at the receptor level and beyond are "what the drug does to the body." These are termed "pharmacodynamic" – when two or more drugs combine to produce the effect (e.g., serotonin syndrome)

Red Flag Drugs - know which CYPs 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)

CYP Genetics

- If the CYP docking site is “faulty” so that Drug C can’t 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)

What CYPs and important in drug metabolism and where are their genes?

- 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

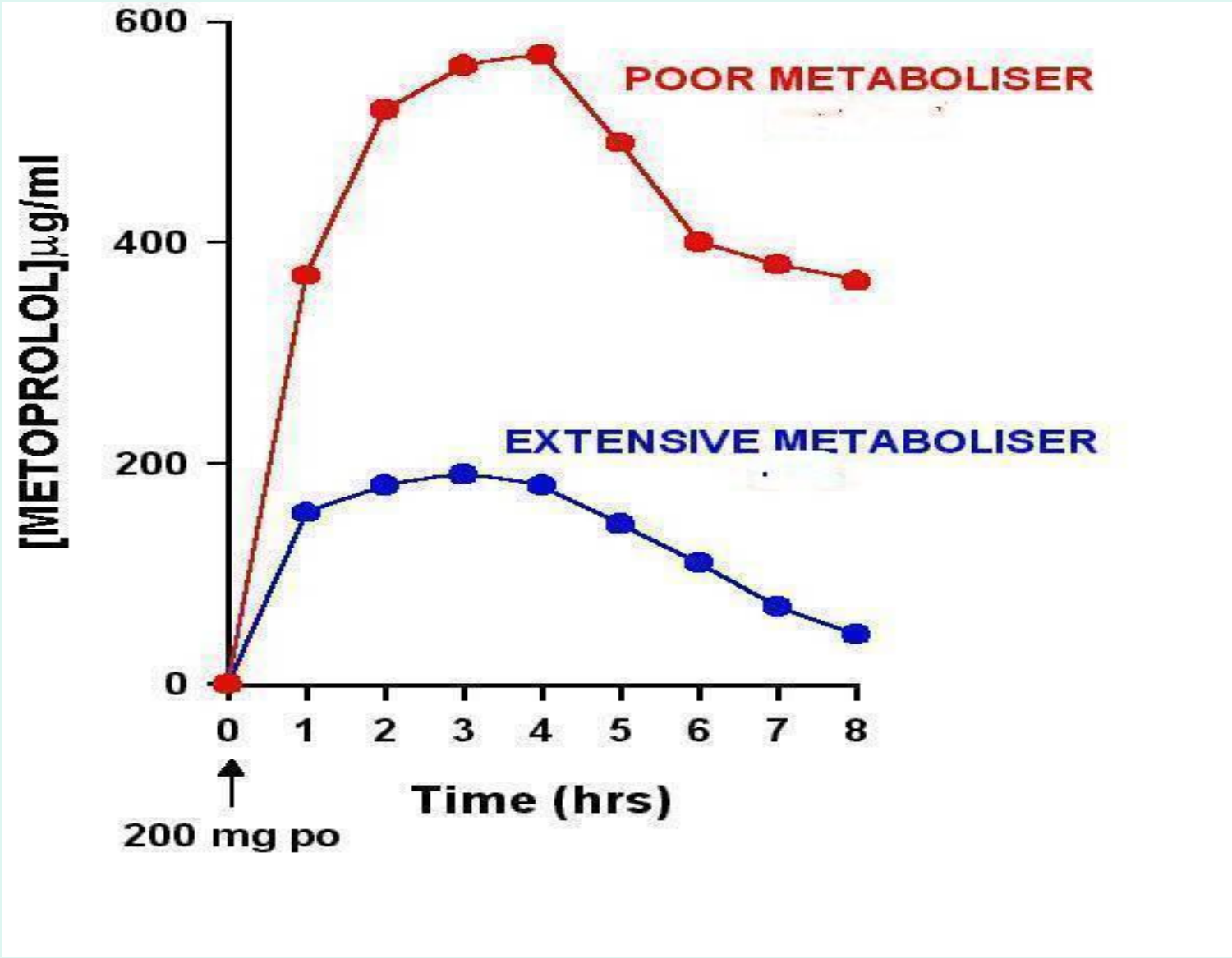
- *Poor Metabolizers*
  - lack functional enzyme.
- *Intermediate Metabolizers*
  - heterozygous for one functional and one deficient allele
  - have two partially defective alleles that cause reduced metabolism
- *Extensive Metabolizers*
  - two normal alleles
  - often majority of population
  - "normal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

Genetic polymorphisms, or "Ethno-psychopharmacology"*

- CYP2D6 poor metabolizers (PM) found in 7-10% of whites and African Americans and 1% Asians. The allele *3,4,5 has major genetic polymorphism with PM = 90 %
- CYP2D6 Ultraextensive Metabolizers - 20% of Saudis/Ethiopians – perhaps due to survival value of ability to detoxify plants during famines
- CYP2C19 has genetic poor metabolizer variants that are clinically important: CYP2C19*2, *3 in 18-23% Asians, 2-5% Caucasians
- CYP2C9*2 and*3 present in about 7% of Caucasians and much less frequent in Asians or African-Americans

* Book by Ng CH et al. Cambridge University Press, 2008

Example of Clinical Implications of CYP2D6 polymorphic 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%) = Gilbert's syndrome with fluctuating hyperbilirubinemia and increased systemic levels of other substrates
- Total absence of UGT1A1 = Criglar-Najjar syndrome

Genetics of Gilbert's Syndrome

- The most common reduced activity gene in Europeans is UGT1A1*28, in which there are 7 thymine-adenine (TA) repeats in the promotor region. The normal or "wild type" gene has six TA repeats and is designated UGT1A1*1.
- The longer the repeat sequence, the slower the enzymatic activity
- If the *28 is on one chromosome, the activity is reduced 25%; if on both, it is reduced 70%

Let's look at the CYP Chart and practice figuring out some interactions

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

Vignette involving 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.

This is a CYP1A2 DDI

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

Another Vignette with 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 subtracting an inducer

Vignette involving CYP2B6

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

Answer

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

Vignette about 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 15th tax season). After symptoms of indigestion and heartburn in late March, internist prescribed omeprazole 20 mg/day. A 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 + nortriptyline). Bupropion XL 300 mg is added and she 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?

This was an example of a **pro-drug** (metabolized by CYPs) added to an inhibitor. Check CYP2D6 column on CYP chart.

Some other CYP **pro-drugs**: codeine, mestranol and desogestrel-containing oral contraceptives

Vignette on CYP3A4

- Patient is on carbamazepine (CBZ) and levels are steady at 6 meq/L. 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 CBZ 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

Another 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.
- See next two slides for the explanation

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 several pathways. One is via CYP2E1 to N-acetyl-p-amino benzoquinone, which is a hepatic toxin.
- Chronic ingestion of alcohol induces CYP2E1.
- Since CYP2E1 is induced, more acetaminophen goes to the toxic metabolite.
- This was not an overdose attempt!

One Example of a UGTs DDI: Lamotrigine (LTG) Metabolism

VPA inhibits
UGT2B7 (UGT1A4=another pathway)

LTG ⟶ LTG-glucuronide

OCs induce

Lamotrigine metabolized by UGT2B7. Levels increased by valproate (VPA), and reduced by oral contraceptives (OCs)

Also valproate levels are reduced by OCs.

There will be fluctuating levels if week-free OCs used

Strategies when using OCs and lamotrigine or valproate

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

In Conclusion:
Nobody can remember all of the DDIs

- But, first find out ALL the drugs the patient is taking, including over-the-counter (OTCs), herbals
- Ask - is there anything I shouldn't be prescribing?
- Narrow your personal formulary and learn the CYP pathways of the drugs you use commonly
- Use the CYP Chart
- Learn the quantity of effects of the major DDIs (eg., paroxetine increases desipramine levels 400% vs. sertraline raises desipramine levels only 25%)

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

On a patient visit

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

- a narrow therapeutic index (valproate, theophylline, carbamazepine)
- causes serious side effects (prolonged QTc, rhabdomyolysis, lower seizure threshold, pregnancy harms)
- is a potent inhibitor or inducer (older anticonvulsants, many HIV drugs)
- has a single metabolic pathway
- Is a pro-drug

Post-Lecture Exam Question 1

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Answers to Questions

1. D
2. E
3. B
4. A
5. A