

# Drug interactions "101"

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# Presentation outline

- Introduction
- CYP450 drug-drug interactions
- Other drug interaction issues
- Q&A

Many factors influence the outcome of drug interactions

## Patient Factors

Genetics  
Diseases  
Diet/Nutrition  
Environment  
Smoking  
Alcohol

## Drug Factors

Dose  
Duration  
Dosing Times  
Sequence  
Route  
Dosage Form

CLINICAL  
OUTCOME  
OF DRUG  
INTERACTIONS

HIGH VARIABILITY



## When are drug-drug interactions likely?

- Enzyme inhibitor/inducer on board
- Drugs with low therapeutic index on board
- Drugs with a multiplicity of pharmacologic actions
- High-risk populations
  - elderly
  - debilitated
  - substance abusers

# Potential Costs of Drug-Drug Interactions

- **Poorer outcomes**
  - increased adverse effects
  - altered pharmacologic response
- **Greater monitoring/assessment**
  - dosage titration
    - ◆ may be difficult because expected response unpredictable
  - side effect detection and management
  - therapeutic drug monitoring
- **Increased medical costs**
  - toxicity
  - destabilization of specific & associated medical conditions

Adapted from P Masand

# Why are drugs metabolized in the first place?

- To increase water solubility in order to facilitate excretion
  - phase I: misc. oxidation reactions
    - ◆ hydroxylation
    - ◆ O-demethylation
    - ◆ N-dealkylation
  - phase II: glucuronidation (often subsequent to phase I)

# Cytochrome P-450 nomenclature

CYtochrome P450 = CYP

CYPxaz...

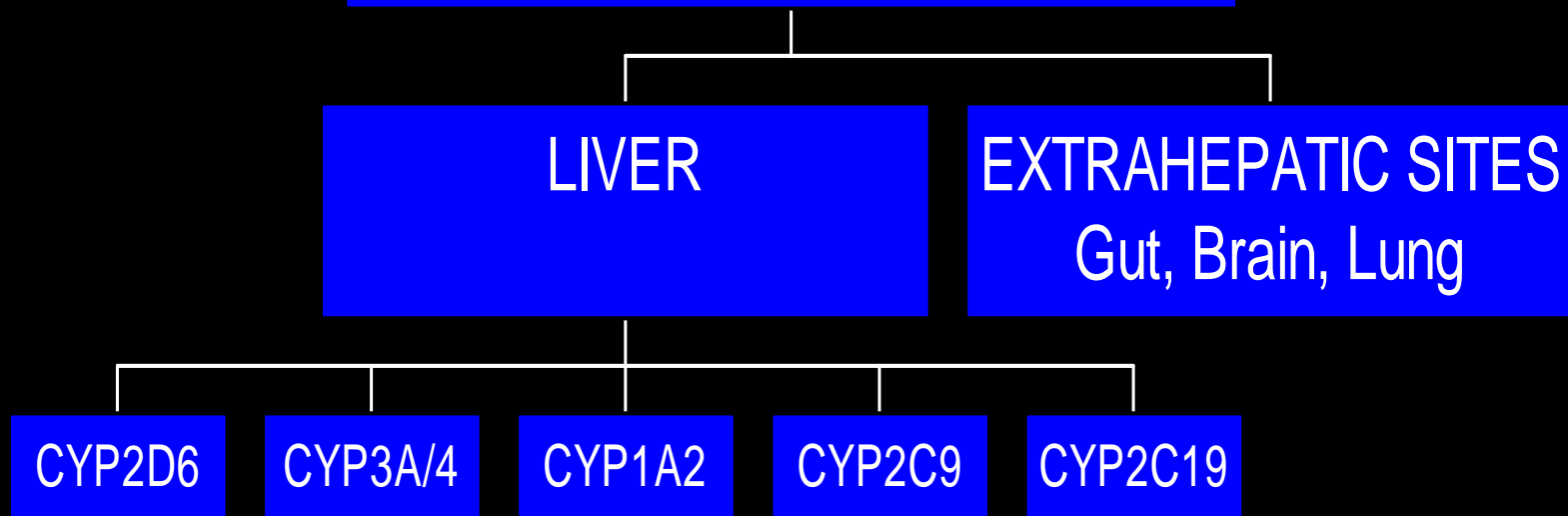
x= numeral indicating isozyme  
family

a= subfamily of isozyme

z= individual enzyme of subfamily

# What is the cytochrome P-450 system?

CYTOCHROME P450 ISOZYMES\*  
12 families identified in mammals  
CYP 1,2,3 impt for drug metabolism



\* heme-containing proteins; heme allows for incorporation of oxygen during biotransformation

# CYP polymorphisms

CYP isozyme	Polymorphism present?
1A2	No
2C9	Yes (2-3% Caucasians, 15-25% Asians)
2C19	?
2D6	Yes (5-8% Caucasians, lower Asians)
2E1	Yes (5-8% Caucasians, lower Asians)
3A4	No

\* 1:10,000 ppl are deficient in both 2D6 and 2C9

Adapted from P Masand

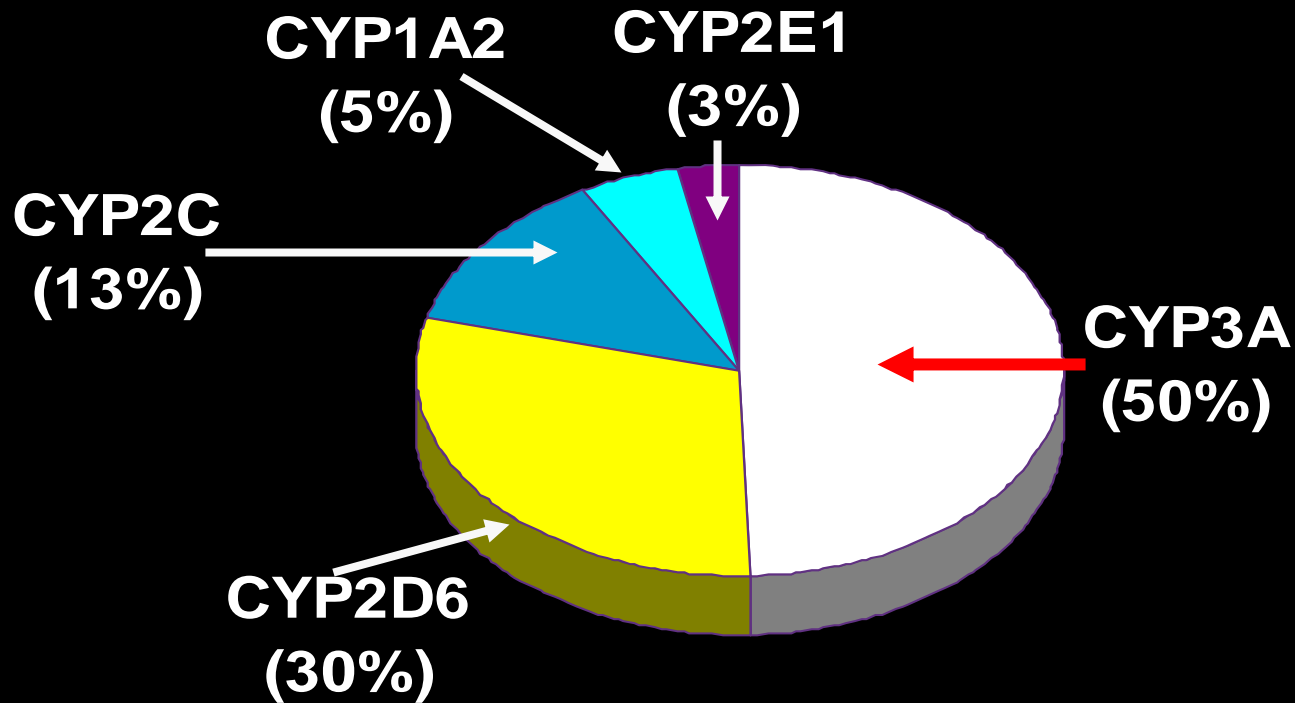
## Sources of variability in drug metabolism

- inter/intraindividual differences in intrinsic enzyme activity
- lack of specific enzyme from genetic mutation (poor metabolizers, or PMs)
  - racial differences in incidence
    - ◆ approx 10% Caucasians are PMs
  - alternative pathways for metabolism?
  - CYP2D6, CYP2C19, CYP2E1
- inhibition/induction of enzyme activity
  - drug- drug, food, smoking, age, disease interactions...
- stereoselective drug metabolism

# Clinical relevance of isozyme genetic polymorphism

- predominantly a problem for PMs
  - toxicity: unmetabolized parent drug accumulation or shunt to pathways producing toxic metabolites
  - efficacy: prodrugs & active metabolites
- drugs which inhibit metabolism may convert extensive metabolizer (EM) to a PM
  - quinidine (2D6); ketoconazole (3A3/4)

# The proportion of drugs metabolized by cytochrome P-450 enzymes



# Hepatic drug-drug interactions simplified

**Drug A** affects **P450 isozyme(s)**

**P450 isozyme(s)** metabolize **Drugs X,Y,Z**

**Drug A** affects **Drugs X,Y,Z**

# CYP1A2

“phenacetin O-deethylase”

- **Inducers**
  - Cigarette smoking (mild)
  - Charcoal-broiled foods
  - Omeprazole
  - Cabbage
  - Brussel sprouts
- **Inhibitors**
  - Fluvoxamine

# Selected drugs metabolized by CYP1A2

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- methylxanthines (caffeine, theophylline)
- TCAs (amitriptyline, clomipramine, imipramine)
- APAP
- propranolol
- clozapine
- R-warfarin



# CYP2C9/19

2C9= "tolbutamide hydroxylase"; 2C19= "S-mephenytoin hydroxylase"

- **Inhibitors**
  - Fluvoxamine
  - Fluoxetine
  - Sertraline
  - Fluconazole

## Selected drugs metabolized by CYP2C9/19

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- clomipramine, imipramine
- diazepam
- omeprazole
- propranolol
- phenytoin
- tolbutamide
- fluvastatin
- ibuprofen



# CYP2D6

“debrisoquin hydroxylase”

- **Inhibitors**

- Quinidine
- Paroxetine
- Fluoxetine
- Sertraline
- Fluvoxamine
- Phenothiazines
- Vincristine
- Diltiazem

**high affinity,  
low capacity**

**saturable pathway**

## Selected drugs metabolized by CYP2D6

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- TCAs (amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, trimipramine)
- IC antiarrhythmics (flecainide, propafenone)
- antipsychotics (clozapine, haloperidol, risperidone)
- beta-blockers (e.g. metoprolol, propranolol)
- opiates (codeine, dextromethorphan)
- SSRIs (fluoxetine, norfluoxetine, paroxetine)
- venlafaxine



# CYP3A4

"cortisol hydroxylase"

- **Inducers**

- Glucocorticoids
- Rifampin
- Phenytoin
- Carbamazepine

- **Inhibitors**

- Nefazodone
- Fluvoxamine
- Ketoconazole
- Itraconazole
- Erythromycin
- Sertraline
- Grapefruit juice

**low affinity,  
high capacity**

## Selected drugs metabolized by CYP3A4

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- antiarrhythmics (lidocaine, propafenone, quinidine)
- carbamazepine
- nefazodone
- BZDs (alprazolam, triazolam, midazolam)
- CCBs
- cyclosporine
- nonsedating antihistamines (terfenadine, astemizole)
- sertraline
- clozapine
- lovastatin, simvastatin, atorvastatin



# CYP2E1

- **Inducers**
  - acute intoxication with alcohol
  - isoniazid
- **Inhibitors**
  - fluvoxamine
  - disulfiram
- **Substrates**
  - alcohol
  - caffeine

# Rules of thumb for assessing the clinical relevance of drug-drug interactions

Clinical relevance	Change in SDC
NCS	<20%*
Mild	20-50%
Moderate	50-150%
Severe	>150%**

\* like missing a dose

\*\* like giving approx 2.5 times usual dose

Preskorn, 1996

# Buildup of SDC due to inhibition of clearance

...TOXICITY: increase in the incidence/ severity of ADRs

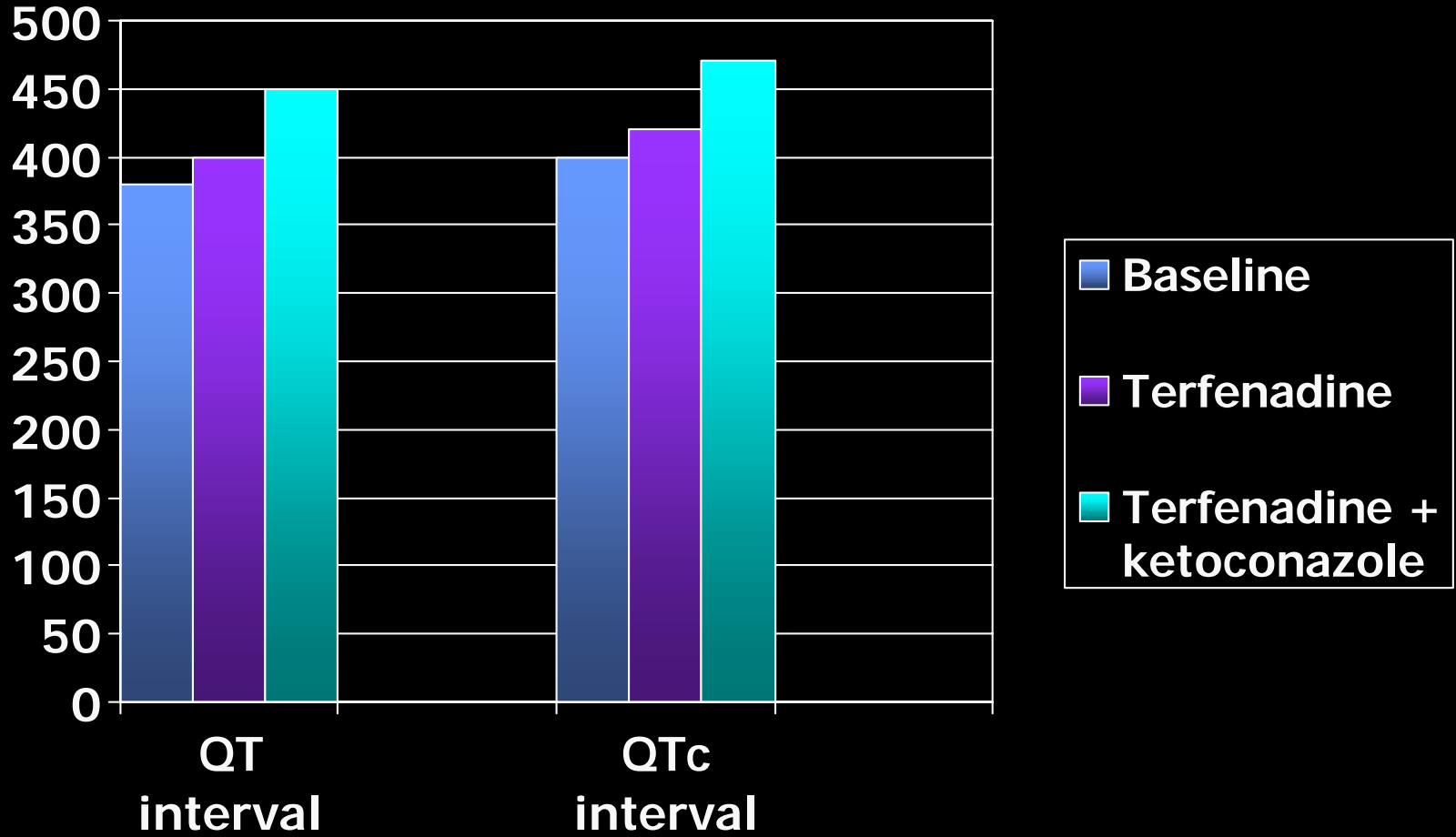
<i>Affected drug</i>	<i>Causative drug</i>	<i>P-450 enzyme</i>
carbamazepine	erythromycin	3A3/4
dextromethorphan	paroxetine	2D6
phenytoin	fluoxetine	2C9/10
propranolol	cimetidine	1A2; 3A3/4
theophylline	fluvoxamine	1A2
TCA's	fluoxetine	2D6
TCA's	fluvoxamine	1A2; 3A3/4
warfarin	fluvoxamine	1A2

# Accumulation of parent drug and/or metabolite

...**TOXICITY**: unexpected ADR based on usual pharmacology of drug

<i>Affected drug</i>	<i>Causative drug</i>	<i>P-450 enzyme</i>
astemizole terfenadine cisapride	ketoconazole erythromycin	3A3/4

# Cardiotoxicity with terfenadine, astemizole, cisapride with potent CYP3A inhibitors



# Reduction in SDC due to induction of clearance

## ... resulting in LOSS OF EFFICACY

<i>Affected drug</i>	<i>Causative drug</i>	<i>P450 enzyme</i>
disopyramide neuroleptics	phenytoin	3A3/4
OCs	carbamazepine	3A3/4
theophylline	phenytoin	1A2
propranolol	rifampin	3A3/4
quinidine	phenobarbital	3A3/4
warfarin	secobarbital	1A2

Preskorn S. Clinically relevant pharmacology of SSRIs  
Caddo, Oklahoma. Professional Communications, Inc.; 1996

# Blockade of the production of an active metabolite

## ...LOSS OF EFFICACY

<i>Affected drug</i>	<i>Causative drug</i>	<i>P-450 enzyme</i>
codeine	paroxetine	2D6

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# Other drug interaction issues

## PK & PD Implications of P-Glycoprotein Modulation

- membrane-associated protein capable of transporting drugs and/or endogenous substances
- recognizes a broad range of pharmacologically and structurally diverse compounds
  - Substrates are large (MW > 300 Da), lipophilic, tend to be cationic at physiologic pH
- expressed in **intestine, liver, kidney, CNS** and **hematologic cells** in humans
- Verapamil, cyclosporine, erythromycin, ketoconazole, tamoxifen, quinidine are P-gp **inhibitors**
- Rifampin, St. John's Wort are P-gp **inducers**

## More on P-gp...

- P-gp and CYP3A4 share many substrates and inhibitors and have a common tissue distribution
  - CYP3A4 accounts for ~70% of total CYP activity in intestine
  - P-gp may work in concert to reduce systemic exposure to certain xenobiotics
  - In the intestine, a substrate for both CYP3A4 and P-gp entering an enterocyte may be absorbed into systemic circulation, metabolized by CYP3A4 in the enterocyte, or secreted back into the intestinal lumen by P-gp... substrate can then be reabsorbed at a distal site and exposed again to the same processes...ENTEROENTERIC RECYCLING
  - In the liver, P-gp is located on the canalicular membrane of hepatocyte ("bile side") and functions to transport substrates into the canalicular space from the interior of the hepatocyte; substrates may be reabsorbed from the intestine... ENTEROHEPATIC RECYCLING... or eliminated in the feces

## Many unanswered questions...

- Very little is known regarding species differences in P-gp function, expression, and regulation
  - A validated animal model with relevance to humans is lacking
- Unknown: effects of gender, age, ethnicity, genetic background, smoking and disease states on P-gp expression and function
- Also unknown: up- and down-regulation of P-gp expression may be an important mechanism underlying numerous drug-drug interactions

# Herbals/ "complimentary therapies"

- Chromium
- Dong quai
- Echinacea
- Ephedra
- Garlic
- Ginger
- Ginko
- Ginseng
- Glucosamine.  
chondroitin
- Green tea
- Kava
- Saw palmetto
- St. John's Wort
- Valerian

**Three words: little supporting data!!**

# A Short History of Medicine

**"I have an earache..."**

- 2000 B.C.**      “Here, eat this root.”
- 1000 A.D.**      “That root is heathen. Here, say this prayer.”
- 1850 A.D.**      “That prayer is superstitious. Here, drink this potion.”
- 1940 A.D.**      “That potion is snake oil. Here, swallow this pill.”
- 1985 A.D.**      “That pill is ineffective. Here, take this antibiotic.”
- 2000 A.D.**      “That antibiotic is artificial. Here, eat this root.”

**Anon**

# Antacids and H-2 antagonists

- Antacids
  - Avoid Mg-containing antacids with renal dx
    - Look for “magnesium hydroxide”, “magnesium oxide” alone (MOM) or in combination (Maalox®)
  - Can decrease absorption of iron salts, quinolones (e.g. Cipro), ketoconazole, tetracyclines, digoxin, isoniazid, phenytoin, quinidine
    - Space dosing by 2 hrs
- H-2 antagonists (Tagamet®, Zantac®, Pepcid®, Axid®)
  - Avoid in nursing mothers
  - Cimetidine (Tagamet®): caution if taking warfarin, theophylline, quinidine, alcohol, caffeine, benzodiazepines

# Counting up your APAP & ASA mgs

- APAP (acetaminophen, Tylenol®)
  - Many medications, especially multi-ingredient cough & cold products, pain and allergy meds also contain aspirin or acetaminophen...total daily maximum for acetaminophen ✂ 4000 mg/day (4 grams/day)
    - Chronic alcoholics and heavy drinkers should limit acetaminophen intake to ✂ 2000mg/day (2 grams/day)
- ASA (aspirin, Bayer®)
  - Avoid in children and adolescents: **Reye's syndrome**
  - Avoid antacids within 2 hrs of taking enteric coated products
  - May cause GI upset, take with food or milk
  - Be aware of other OTC & Rx products containing ASA... pain, cough, cold, allergy
  - **Inform MD or DDS prior to surgery or dental procedure**

# OTC cough and cold preps

*get a flu shot!*

- Remember APAP and ASA content
- Decongestants= sympathomimetics= **caution in pts with CV disease**
- Antihistamines= many help to dry secretions, **often just fatigue you!**
  - Caution in elderly, narrow angle glaucoma
- Antitussives (Robitussin®)... OTC not that effective, drinking plenty of H<sub>2</sub>O may be just as effective!
- Zinc: **a waste of money!**

**Do you really need that combo product?**

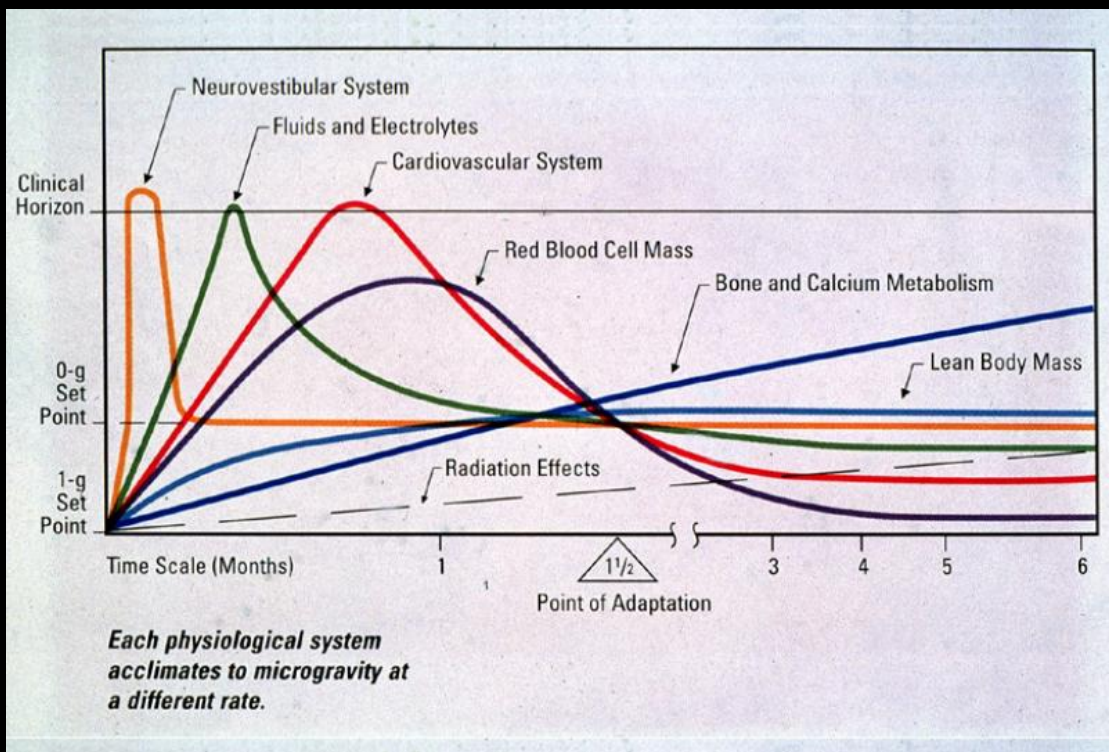
# Key summary points

- CYP450 interactions
  - Inhibitors increase SDCs of other drugs &/or metabolites
  - Inducers decrease SDCs of other drugs
  - There is variability among medications in terms of what P-450 enzymes they inhibit & to what extent
  - Knowledge of key enzymes improves clinical decision-making & rational prescribing
- Other interactions

Adapted from Preskorn, 1996

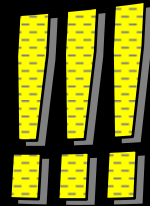
Since I AM at NASA,  
after all...

# Implications for microgravity drug administration



Prevention of drug-drug interactions

**ASK QUESTIONS**



Questions?

