PainWeek®

It's a Pharmaceutical Festival!
Doing a Deep Dive Into Drug Interactions!

Part 2

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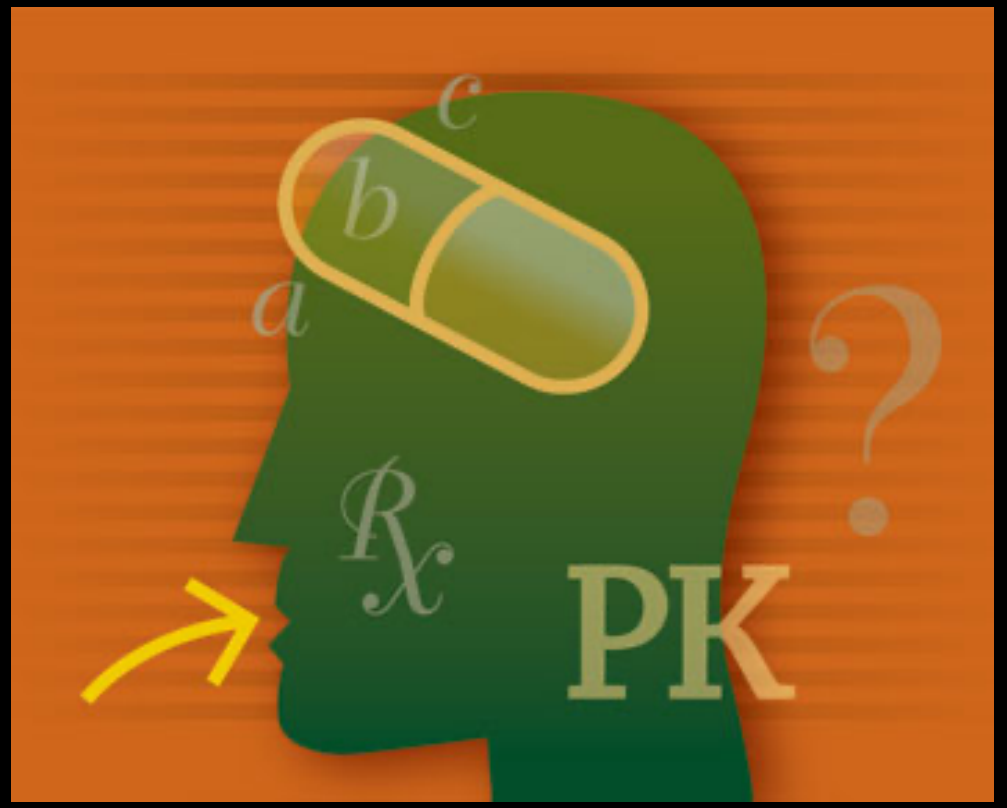
Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion



Drug Metabolism

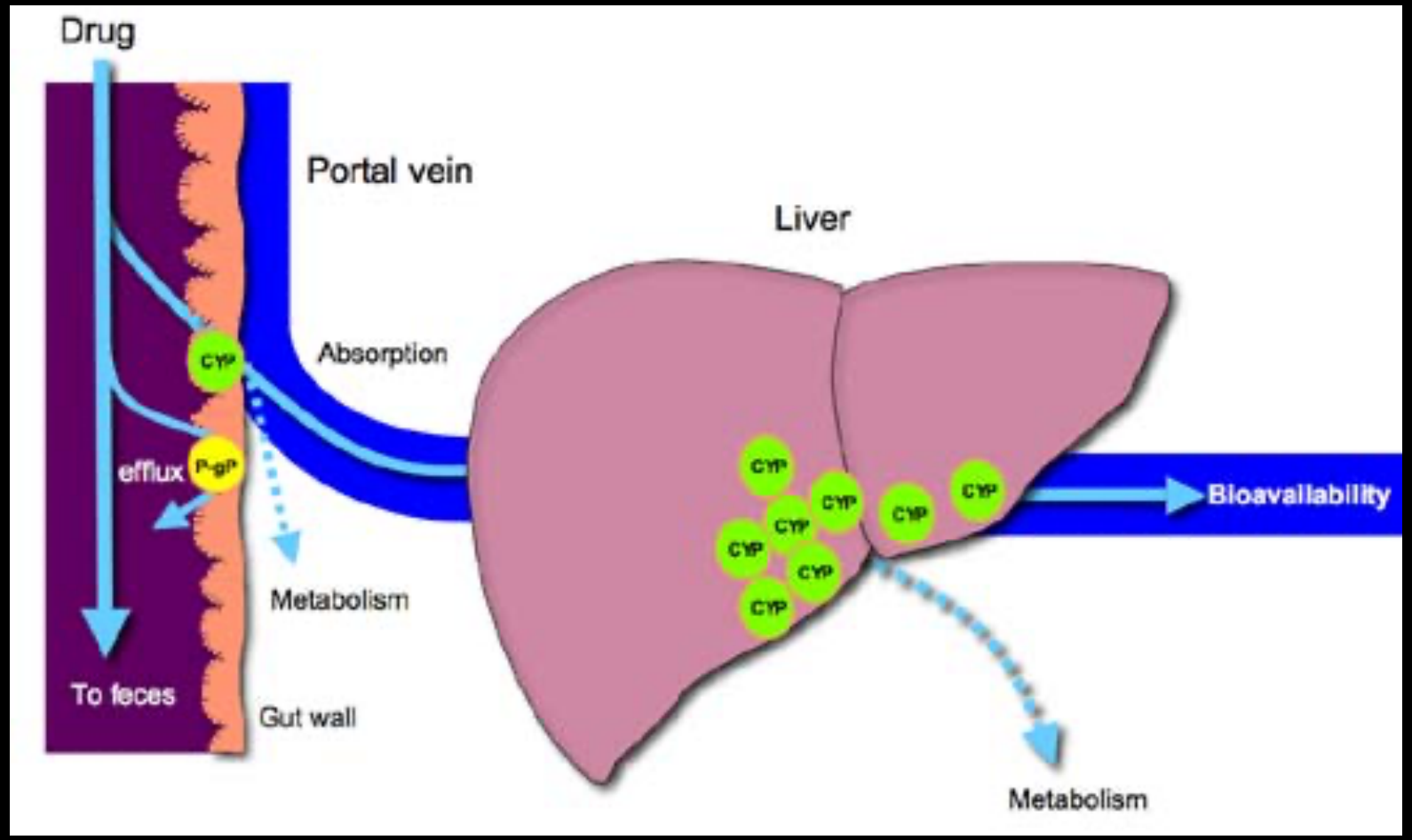
- Metabolism is characterized by two phases of enzymatic reactions which make the drug more water soluble to facilitate elimination from the body
  - Phase I (biotransformation)
    - Oxidation, hydroxylation, reduction, hydrolysis
    - Chemical modification to add a functional group
  - Phase II (conjugation)
    - Functional group used to attach a conjugate
    - Acetylation, glucuronidation, sulfation, methylation

Cytochrome P450 System

- A very large and diverse superfamily of heme-containing proteins
  - Founds in mammals, birds, fish, insects, worms, sea squirts, sea urchins, plants, fungi, slime molds, bacteria and archaea
- The cytochrome P450 system
  - Drug-metabolizing enzymes
  - Enzymes that are used to make cholesterol, steroids, and other lipids (prostacyclins, thromboxane A2)

Cytochrome P450 System

- "Cytochrome P450"
  - They are colored ("chrome")
  - Cellular ("cyto") proteins
  - With a pigment (P) at 450 nm
- Humans have 18 families of cytochrome P450 genes and 44 subfamilies
- Major site of drug-metabolizing enzymes
  - Liver (hepatocytes) and small intestine (enterocytes)
- Minor sites include kidneys, lungs, brain



Drug = substrate

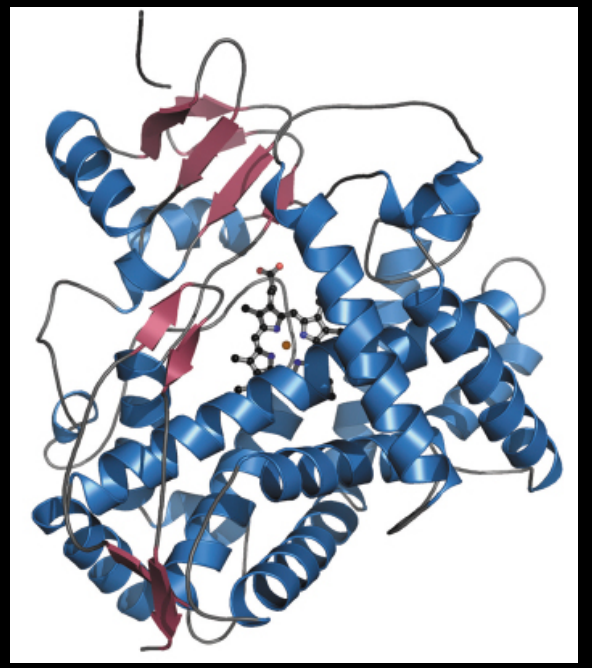
Cytochrome P450 Nomenclature (e.g., CYP2D6)

- CYP = cytochrome P450 (root)
- 2 = genetic family
- D = genetic sub-family
- 6 = specific gene
  - –All CYP isoenzymes in the same family have at least 40% structural similarity
  - –All member in the same subfamily have at least 60% structural similarity
- NOTE that this nomenclature is genetically based: it has NO functional implication

www.fda.gov/cder/drug/drugReactions/

Major CYP450 Enzymes

- More than 90% of human drug metabolism is due to six CYP isoenzymes
  - 1A2
  - 2C9
  - 2C19
  - 2D6
  - 2E1
  - 3A4



Spectrum of Drug Metabolism Consequences

- Inactive products
- Active metabolites
- Similar to parent drug
- More active than parent drug
- New action
- Toxic metabolites

Alteration in Drug Metabolism

- May alter consequences of drug metabolism
- Altered activity may be due to
  - Interacting drugs that increase or decrease inherent enzyme activity
  - Inter-individual capability of metabolic enzymes
    - Genetic differences in enzyme activity (poor metabolizers up to ultra-rapid metabolizers)
  - Other patient factors
    - Gender, hormonal status, age (infants, older adults), pre-existing co-morbid conditions (liver impairment, prolonged Q-T interval, infection)

Alteration in Drug Metabolism

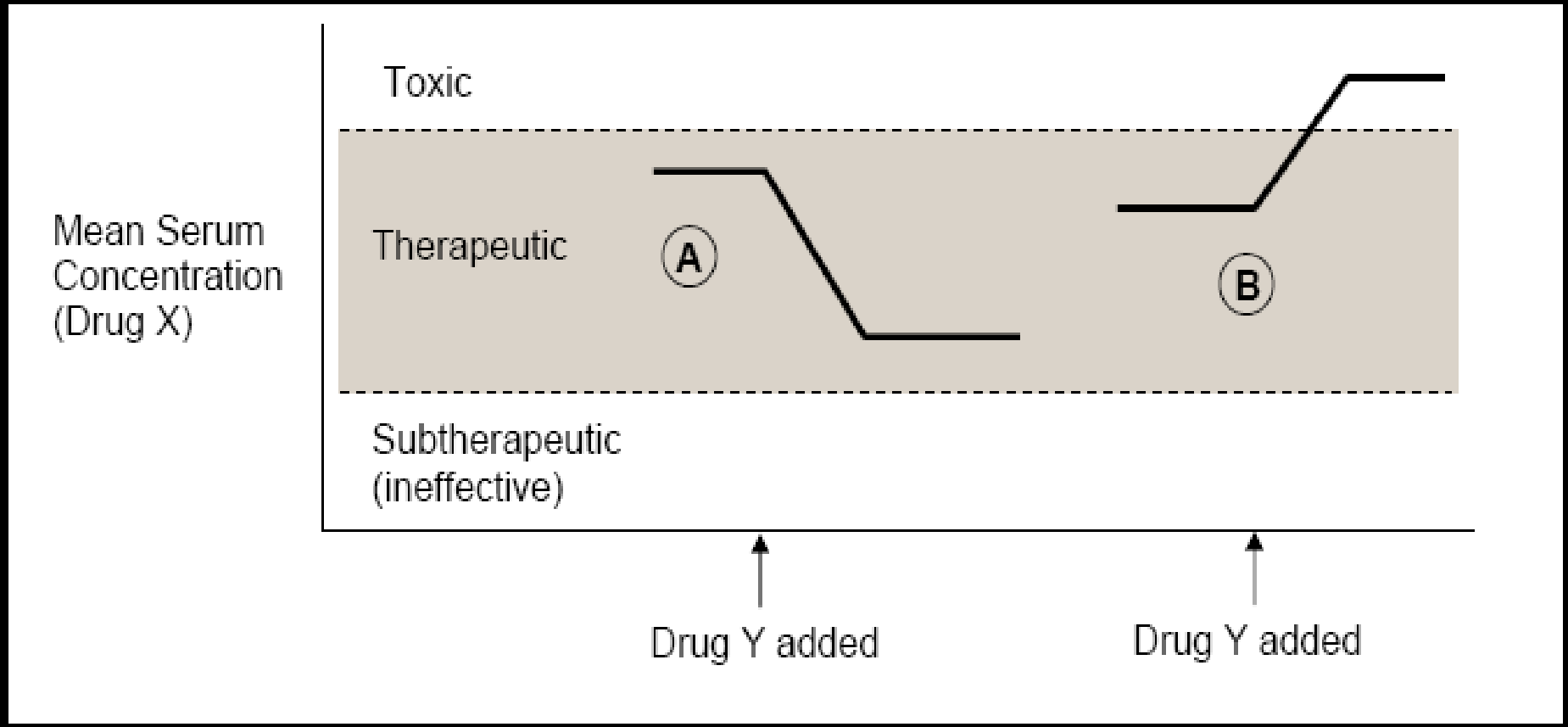
- Substrate – a compound that is metabolized by a given enzyme
  - Fluoxetine (substrate) is metabolized by CYP2D6 and CYP3A4
    - More than one enzyme can metabolite a single agent
    - If one enzyme system is shut down (or otherwise altered) the other can still metabolize fluoxetine

Alteration in Drug Metabolism

- Inhibitor – a compound that “slows down” the metabolism of a substrate by a given enzyme
  - Fluoxetine (inhibitor) slows down the metabolism of desipramine (substrate) by CYP2D6
  - Causes desipramine levels to rise
  - Can have adverse clinical consequences
    - Arrhythmias
    - Possibly fatal

Alteration in Drug Metabolism

- Inducer – a compound that “speeds up” the metabolism of a substrate by a given enzyme
  - Carbamazepine (inducer) speeds up the metabolism of clozapine (substrate) by both CYP1A2 and CYP3A4.
  - Clozapine plasma levels will fall
  - If carbamazepine is discontinued, clozapine levels will rise



A – an inducer (Drug Y) was added to drug regimen (Drug X)
B – an inhibitor (Drug Y) was added to drug regimen (Drug X)

Enzyme Induction and Inhibition

- Enzyme induction usually takes days to weeks to occur
  - –Common enzyme inducing agents include:
    - Barbiturates (phenobarbital)
    - Anticonvulsants (CBZ, phenytoin, primidone)
    - Rifampin
- Enzyme inhibition usually occurs within 24 hours
  - –Common enzyme inhibiting agents include:
    - Ketoconazole
    - Cimetidine

Herb-Drug Interaction

- Grapefruit juice – a selective inhibitor of intestinal metabolism
  - Inhibits CYP3A enzymes in intestinal cells (minimal effect on hepatic CYP3A enzymes)
  - BAB felodipine increased from 14.2% with water to 25.3% after grapefruit juice
  - One glass of juice per day x 3 days doubled serum concentrations of lovastatin
  - Three glass per day resulted in a 15-fold increase in lovastatin and simvastatin serum concentrations

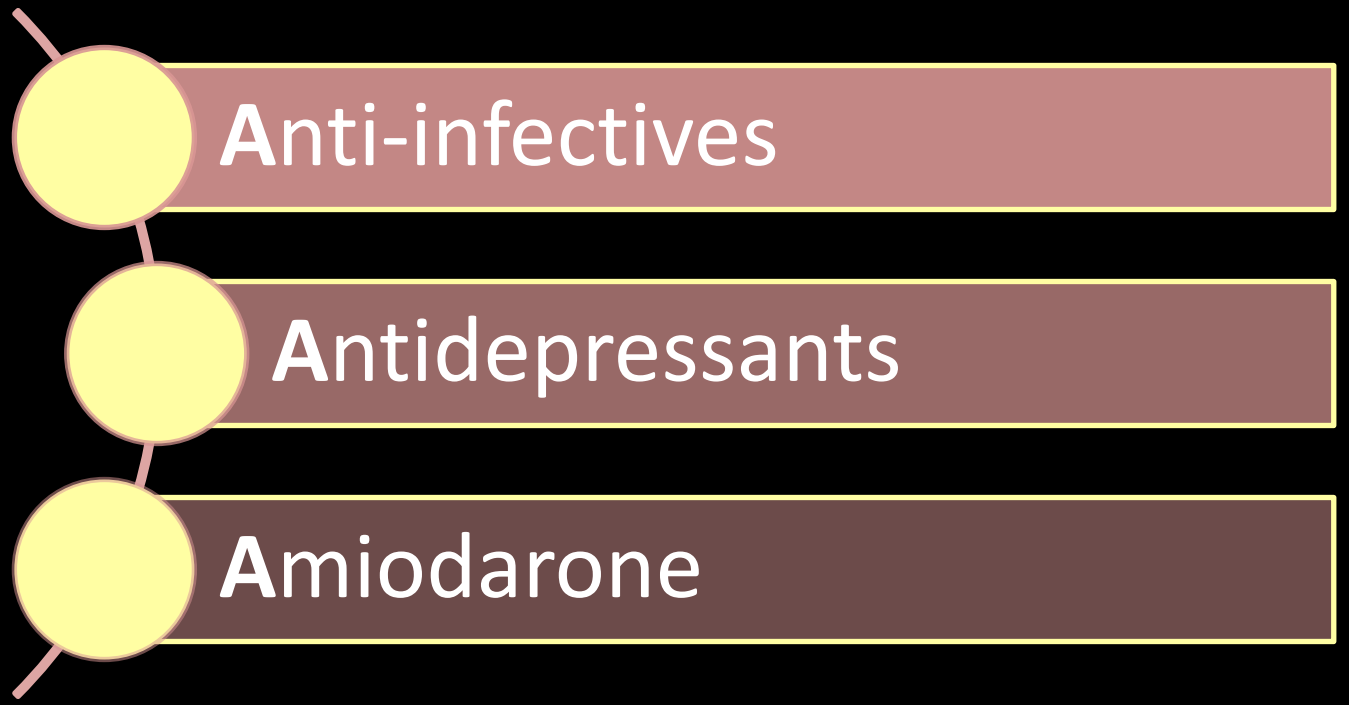
Methadone

- Primarily metabolized by N-demethylation to an inactive metabolite:
  - 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP)
- Metabolized by
  - CYP3A4, CYP2B6, and CYP2C19
  - To a lesser extent CYP2C9 and CYP2D6

Effect of Enzyme Inhibitors/Inducers

What's the situation?	What happens in this situation?	What does this mean for my patient?	What should I do about it?
Taking methadone with medications known to be enzyme inhibitors	Slowed metabolism of methadone, resulting in increased methadone serum level	The patient may become toxic from a methadone overdose	Reduce calculated methadone dose by 25% or more. Encourage use of rescue opioid.
Taking methadone with medications known to be enzyme inducers.	Increased metabolism of methadone, resulting in decreased methadone serum level	Dose of methadone may be insufficient and patient can experience increased pain	Use calculated methadone dose but strongly encourage use of rescue opioid. Increase methadone if appropriate once at steady-state.

Drugs that Inhibit Methadone Metabolism



Enzyme Inducers	Enzyme Inhibitors	
Rifampicin / rifampin	**Amiodarone**	Ketoconazole
Rifabutin	Fluconazole	Erythromycin
Phenobarbital	Fluoxetine	Troleandomycin
Phenytoin	Paroxetine	Citalopram
Spironolactone	Sertraline	Desipramine
Nevirapine	Ciprofloxacin	Clarithromycin
Efavirenz	Fluvoxamine	Telithromycin
Amprenavir	Amitriptyline	Itraconazole
Nelfinavir		
Ritonavir		
Carbamazepine		
St. John's Wort		

Anti-infectives
- Antibiotics
- Antifungals
- Antivirals

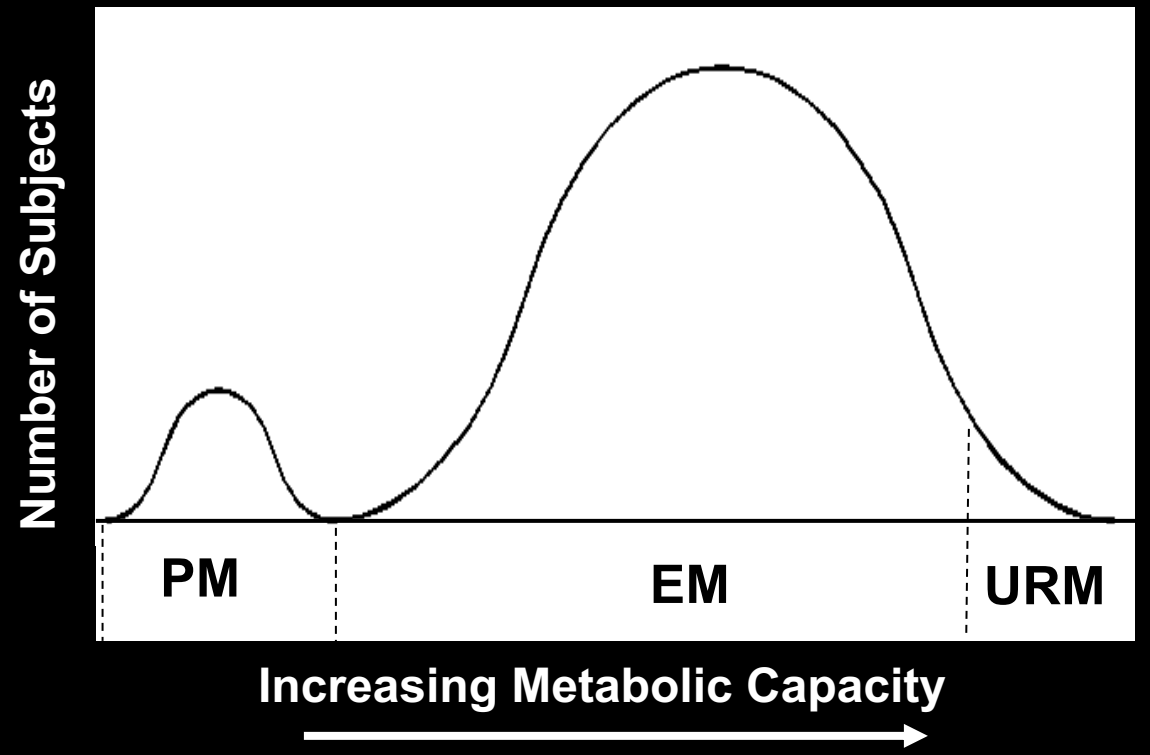
Antidepressants
- SSRIs
- TCAs

Amiodarone

One size really DOESN’T fit all!

Polymorphic Distribution

- A trait that has differential expression in >1% of the population



Differences in metabolizer status among racial (ethnic) groups

Gene or enzyme	Phenotype	Frequencies
CYP1A2	PM	Caucasians 12%
CYP2C9	PM	Caucasians 2-6%
CYP2C19	PM	Caucasians 2-6%
		Chinese 15-17%
		Japanese 18-23%
CYP2D6	PM	Caucasians 3-10%
		Chinese/Japanese/ AA < 2%
	UR	Ethiopians 20%
		Hispanics 7%
		Scandinavians 1.5%

PM – poor metabolizer
UR – ultra-rapid metabolizer

Examples in Palliative Care

- Acetaminophen overdose
- CYP2E1 converts acetaminophen to a toxic intermediate that can react with cellular macromolecules to damage cells and cause cell death
- This intermediate normally reacts with glutathione, a natural antioxidant in cells
- When glutathione is depleted cell death occurs (3-4 days after the overdose)
- Problem worse with alcoholics, who have hyperfunctioning of the CYP2E1, therefore produce more of the toxic intermediate

Examples in Palliative Care

- Codeine (CYP2D6)
  - Poor metabolizers are unable to convert codeine to morphine (no pain relief)
- Hydrocodone, oxycodone (CYP2D6)
  - Structurally similar to codeine and as such their metabolism could be under genetic control leading to variability of clinical response (side effects, efficacy, and dependence)

Examples in Palliative Care

- Phenytoin (CYP1A2, CYP2C9, CYP2C19)
  - Phenytoin toxicity for poor metabolizers; low levels of drug for ultra-rapid metabolizers at therapeutic doses
- Diazepam (CYP2C19, CYP3A4)
  - Unacceptable prolonged sedation in poor metabolizers, unconsciousness noted more in Asian populations

Examples in Palliative Care

- Venlafaxine (CYP2D6)
  - Metabolism slower in those lacking a functional CYP2D6 gene
- Nortriptyline (CYP2D6, CYP1A2)
  - Ultra-rapid metabolizers require up to 500 mg/day to reach therapeutic dose

Cannabis Drug Interactions

THC

- Metabolized by CYP3A4 and CYP2C9
- CYP1A2 inducer
  - –THC can ↓ serum concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, chlorpromazine

CBD

- –Metabolized by CYP3A4, CYP2C9, CYP2C19
- –Potent inhibitor of CYP3A4, CYP2D6, CYP2C19
  - **3A4:** CBD can ↑ serum concentrations of macrolide antibiotics, calcium channel blockers, benzodiazepines, PDE5 inhibitors, antihistamines, haloperidol, antiretrovirals, some statins
  - **2D6:** CBD can ↑ serum concentrations of SSRIs, TCAs, antipsychotics, beta blockers, and opioids

Cannabis Drug Interactions

- **Buprenorphine**
  - CYP3A4
  - Cannabis ↓ the formation of norbuprenorphine and ↑ buprenorphine and norbuprenorphine concentrations
- **Clobazam**
  - CYP2C19
  - CBD ↑ serum concentrations of clobazam
- **CNS depressants (alcohol, opioids)**
  - Additive effects can be seen (drowsiness, ataxia)
- **Tacrolimus**
  - CYP3A4
  - CBD ↑ serum concentrations of tacrolimus ~3-fold
- **Theophylline**
  - Smoking cannabis ↑ the clearance of theophylline by 40%.
- **Warfarin**
  - CYP2C9
  - ↑ INR and risk of bleeding

Case 1

- Mr. Jones is a 72 year old man with a history of prostate cancer. Over the past week or so he has been complaining of a new pain in his left rib area.
- The pain is very well localized, and he describes it as achy, and considerably worse when he rolls over onto his left side.
- The primary care physician suspects metastatic bone disease, and he orders dexamethasone 4 mg po bid
- Mr. Jones is already taking ibuprofen 800 mg po q6h.
- What do you think of adding dexamethasone?

Case 2

- KS is a 54 year old woman with a diagnosis of end-stage breast cancer. She is receiving methadone 10 mg po q8h with good pain control.
- She has developed thrush, for which her prescriber ordered fluconazole 150 mg po x 1 dose.
- Should we worry about a drug interaction?
- What is the prescriber ordered fluconazole 100 mg po qd x 7 days?

Case 3

- The hospice nurse calls you one day to ask your thoughts about an 84 year old man with a very limited prognosis, receiving methadone 5 mg po q12h with good effect.
- Over the past week however, he has become increasing ataxic and stumbling. He even fell once and hurt his wrist.
- His pain control has worsened as the week has gone on, requiring increased use of his “as needed” morphine.
- What’s going on? The nurse says no medications have been added or taken away?

Case 3

- The nurse finally recalls that the physician had ordered a phenytoin serum level which came back as subtherapeutic.
- The prescriber increased the phenytoin from 300 mg po qd to 500 mg po qd.
- Wow – hold the phenytoin, get a STAT phenytoin level (total AND unbound)!
- What's the dealio?

Conclusion/Summary

- Practitioner who do not consider the ramifications of STARTING or STOPPING medications are naughty kittens
- Drug interactions can be pharmacodynamic or pharmacokinetic
- Your pharmacist is your new best friend!

Additional references

- Falconi G, Kashan S. Drug Interactions In Palliative Care. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; June 1, 2020. Available at https://www.ncbi.nlm.nih.gov/books/NBK551619/
- MacDonald E, Farrah K. *Medical Cannabis Use in Palliative Care: Review of Clinical Effectiveness and Guidelines – An Update*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; October 29, 2019. Available at https://pubmed.ncbi.nlm.nih.gov/31873991/
- Geist M, Bardenheuer H, Burhenne J, Mikus G. Alteration of drug-metabolizing enzyme activity in palliative care patients: Microdosed assessment of cytochrome P450 3A. *Palliat Med*. 2019;33(7):850-855. doi:10.1177/0269216319843629. Available at https://pubmed.ncbi.nlm.nih.gov/31023150/
- Geist MJP, Bardenheuer HJ, Burhenne J, Mikus G. In Vivo CYP3A Activity in Palliative Care Patients: Study Protocol for a Single Arm Prospective Trial. *J Palliat Med*. 2018;21(5):686-688. doi:10.1089/jpm.2017.0461. Available at https://pubmed.ncbi.nlm.nih.gov/29327978/
- Hoemme A, Barth H, Haschke M, et al. Prognostic impact of polypharmacy and drug interactions in patients with advanced cancer. *Cancer Chemother Pharmacol*. 2019;83(4):763-774. doi:10.1007/s00280-019-03783-9. https://pubmed.ncbi.nlm.nih.gov/30684020/

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