

Drug Interactions Among Commonly Prescribed Analgesics

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Disclosures

- Remitigate, LLC

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Objectives

At the completion of this presentation participants will be able to

- Understand Cytochrome P450 (CYP450) role in pharmacokinetics
- Recognize key CYP450 mediated drug-drug interactions
- Identify potential drug-drug interactions and important considerations when prescribing various analgesic classes and adjuvants (antidepressants, anticonvulsants, etc.)

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Common Mechanisms for Drug Interactions

- Similar or overlapping pharmacological activity
 - Opioids / Benzodiazepines and sedation
 - Opioids / TCAs and constipation
 - NSAIDs / SNRIs / Steroids and bleed risk
- Protein binding and free drug
 - NSAIDs and albumin
 - Amitriptyline and alpha-glycoprotein
- CYP induction, inhibition, autoinduction, substrates
 - Carbamazepine/methadone, codeine or tramadol/sertraline
- P-glycoprotein
 - Morphine/rifampin, methadone/telaprevir

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Cytochrome P450 Review

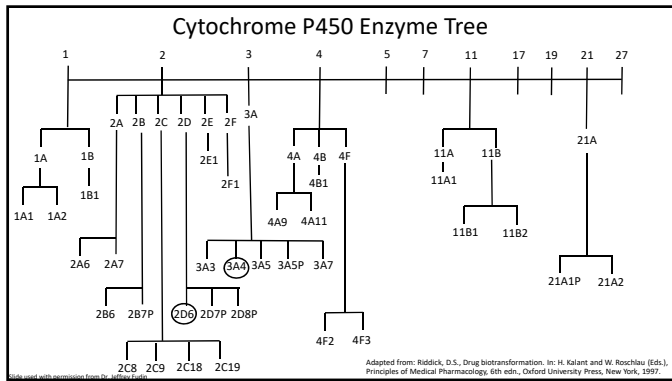
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CYP450 Nomenclature

- Cytochrome is designated CYP
- CYP (#) - # identifying the enzyme family
- CYP (#) (A,C) - Subfamily designation
- CYP (#) (A,C) (#) - Individual enzyme (this is based on when enzyme was discovered)
- EXAMPLES:
 - CYP3A4, CYP2D6, CYP1A2

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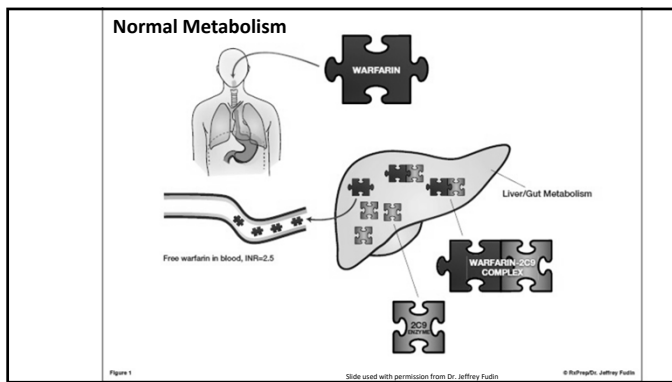


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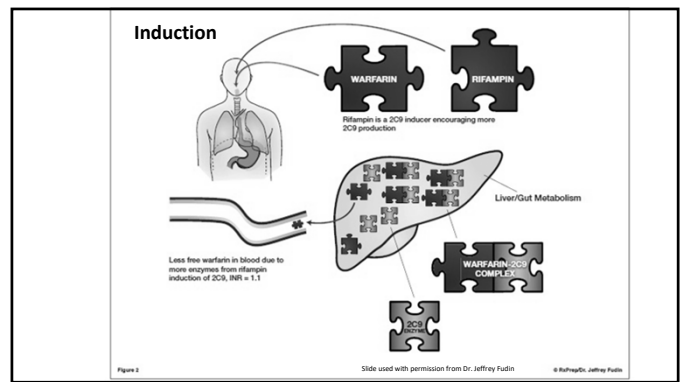
Terminology

- Inducer
 - 3 weeks
- Inhibitor
 - 48 hours
- Substrate
- Genetic Polymorphism
 - Poor Metabolizer
 - Intermediate Metabolizer
 - Extensive Metabolizer*
 - Ultrarapid Metabolizer
- Autoinducer
 - Carbamazepine

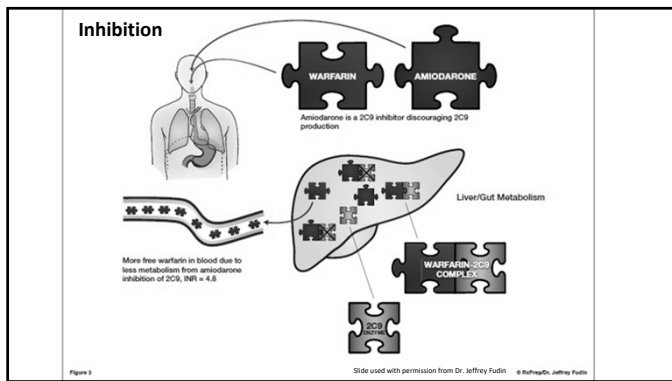
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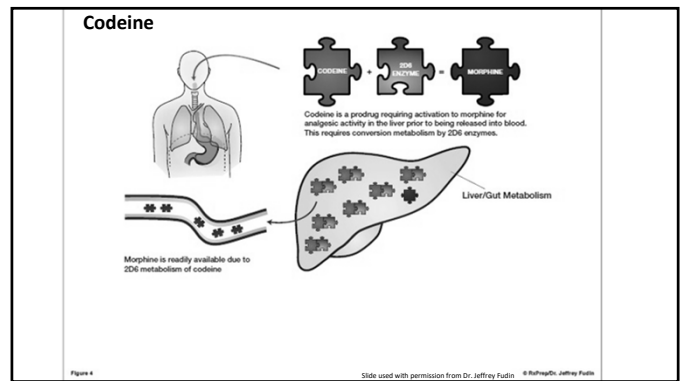
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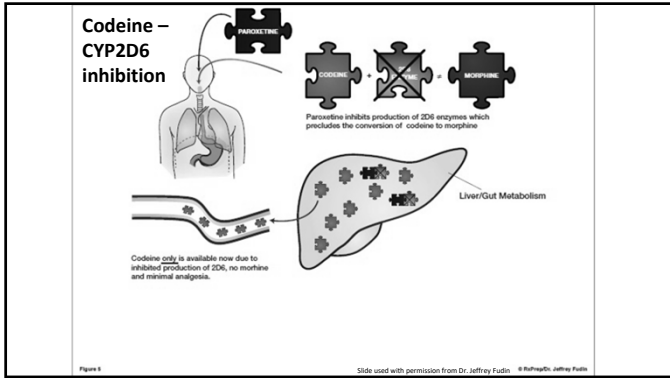
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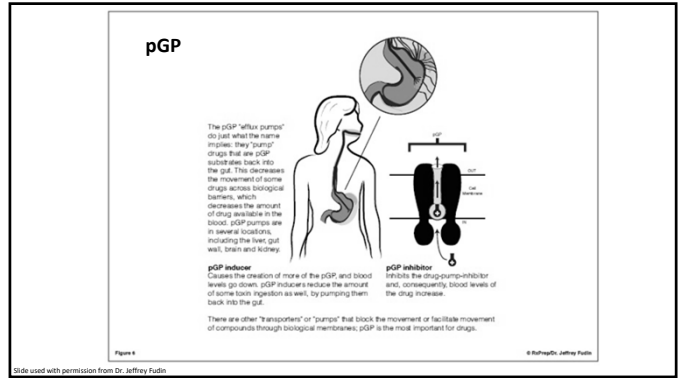
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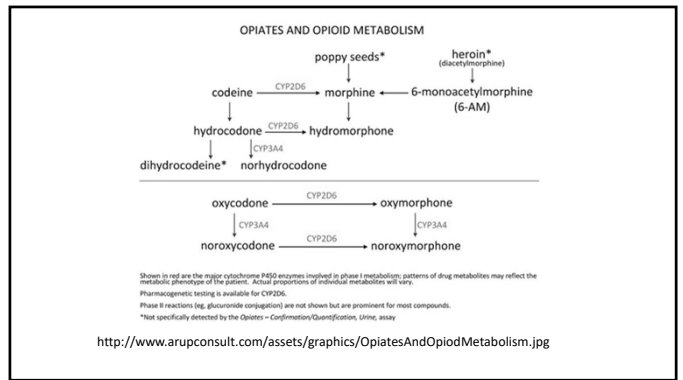
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Opioid Pharmacokinetics and Drug-Drug Interactions

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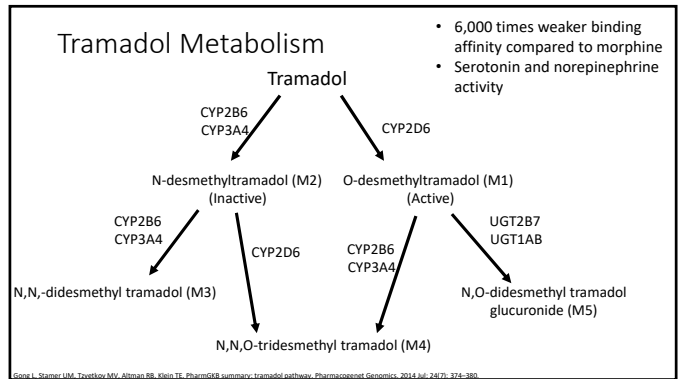
Medication Metabolism

Phase of Metabolism	Key Enzymes Involved	Examples: Opioid Medication Metabolized
Phase I	Cytochrome P450 (CYP450) Examples: CYP2D6, CYP2C19, CYP2B6, CYP2C9, CYP3A4 & CYP3A5	Codeine, hydrocodone, oxycodone, tramadol, fentanyl, methadone, buprenorphine
Phase II	Uridine 5'-diphosphoglucuronosyltransferase (UDP-glucuronosyltransferase, UGT) Examples: UGT2B7 & 2B15	Morphine, oxymorphone, hydromorphone, tapentadol, levorphanol

Smith HS. Opioid metabolism. Mayo Clin Proc. 2009;84(7):613-624.

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Common CYP3A4 Inhibitors

CYP3A4 Inhibitors		CYP3A4 Inducers	
Aprepitant	Grapefruit juice	Barbiturates	Griseofulvin
Amiodarone	Indinavir	Bicalutamide	Nafcillin
Atazanavir	Itraconazole	Carbamazepine*	Oxcarbazepine
Cimetidine	Ketoconazole	Dexamethasone	Phenobarbital
Clarithromycin	Nefazodone	Efavirenz	Phenytoin
Diltiazem	Ritonavir	Etravirine	Primidone
Erythromycin	Telithromycin	Fosphenytoin	Rifabutin
Fluconazole	Verapamil		Rifampin
Fosamprenavir			St. John's Wort

Horn JR, Hansten PD. Get to Know an Enzyme: CYP2D6. *PharmacyTimes*. 1 July 2008. Accessed 6 Mar 2017. Available <http://www.pharmacytimes.com/publications/issue/2008/2008-07/2008-07-0634>

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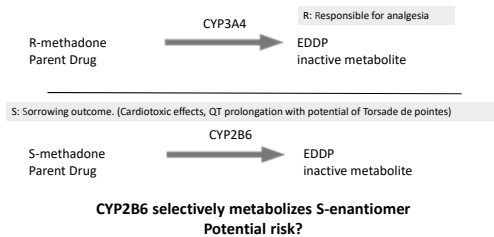
Common CYP2D6 Inhibitors

CYP2D6 Inhibitors	
Amiodarone	Haloperidol
Bupropion	Imatinib
Celecoxib	Paroxetine
Cinacalcet	Quinidine
Diphenhydramine	Terbinafine
Fluoxetine	Thioridazine

- There are no known CYP2D6 inducers
- See similar expected outcome with an ultra-rapid metabolizer

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Methadone Metabolism



Gerber JS et al. Stereoselective Metabolism of Methadone N-Demethylation by Cytochrome P4502B6 and 2C19. *Chirality* 2006;16:36-44. Slide used with permission from Dr. Jeffrey Fudin

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QTc Prolonging Drugs

- Quinolone Antibiotics
- Macrolide Antibiotics
- Amiodarone/Sotalol
- Sertraline/Citalopram
- Venlafaxine
- Fluconazole/Ketoconazole
- Ondansetron
- Quetiapine
- Buprenorphine
- Methadone

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QTc Prolonging Drugs - Buprenorphine

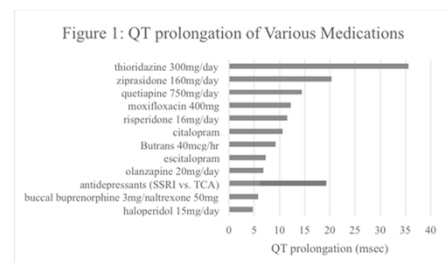
- Buprenorphine Buccal Films (Belbuca)
 - 900mcg Q12H (max dose)
 - QTc 450-480 msec – 2% of patients
 - Up to 9.2msec prolongation
- Butrans Transdermal Patch (Butrans TDS)
 - Max dose 20mcg/hr
 - No QTc prolongation seen in trials at this dose

Fudin J, Pratt Clary J, Gottwald J. A Brief Review of Buprenorphine Products. *PharmacyTimes*. 22 Mar 2016. Accessed 2 Mar 2017. Available from <http://www.pharmacytimes.com/contributor/jeffrey-fudin/2016/03/a-brief-review-of-buprenorphine-products>

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QTc Prolonging Drugs

“Note that these data are not meant to be used for direct comparisons between the various agents because of differences in study design, QT correction strategies, and population variations, but are instead provided as context for the current landscape of QT-prolonging drugs.”



Fudin J, Pratt Clary J, Gottwald J. A Brief Review of Buprenorphine Products. *PharmacyTimes*. 22 Mar 2016. Accessed 2 Mar 2017. Available from <http://www.pharmacytimes.com/contributor/jeffrey-fudin/2016/03/a-brief-review-of-buprenorphine-products>

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Methadone vs Levorphanol

Methodone	Both	Levorphanol
< kappa agonist	Mu-opioid agonist NMDA antagonist	> kappa agonist Delta
CYP 450 metabolism PGP substrate	Norepinephrine reuptake antagonist Serotonin reuptake antagonist	Phase II glucuronidation Not a known PGP substrate
$t_{1/2}$ = 8-60 hours Up to 150 hours in polymorphic outliers		$t_{1/2}$ = 11-16 hours
QTc Prolongation		NO QTc Prolongation

Pham TC, Fudin J, Ruffo RB. Is Levorphanol a Better Option Than Methadone? Pain Medicine. 2015 September; 16(9):1673-1679.

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Non-Opioid Drug-Drug Interactions

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Acetaminophen

- **Metabolism**
 - Pediatrics – sulfation
 - Adults – glucuronidation
 - CYP2E1 – N-acetyl-p-benzoquinone imine (NAPQI)
- **DDIs**
 - Avoid concomitant hepatotoxic therapies
 - Imatinib, dasatinib, and sunitinib – inhibit glucuronidation
 - Max 1,300mg/day
 - Warfarin
 - Possibly: CYP2C9, NAPQI and/or hepatotoxicity
 - INR↑

McGill MR, Jaschke H. Metabolism and disposition of acetaminophen: recent advances in relation to hepatotoxicity and diagnosis. Pharm Res. 2013;30(9):2174-87.
Zhang Q, Bai Q, Solter C, Drouot L, Simonneau G, Alvarez JC, Puvion S, et al. Interaction between acetaminophen and warfarin in adults receiving long-term oral anticoagulants: a randomized controlled trial. Eur J Clin Pharmacol. 2015;47(3):309-14.
Saso-Tenkorsmaa J, Fudin J. Drug Interactions in Cancer Patients Requiring Concomitant Chemotherapy and Analgesics. Practical Pain Management. 2013 May; 13 (6):50-64.

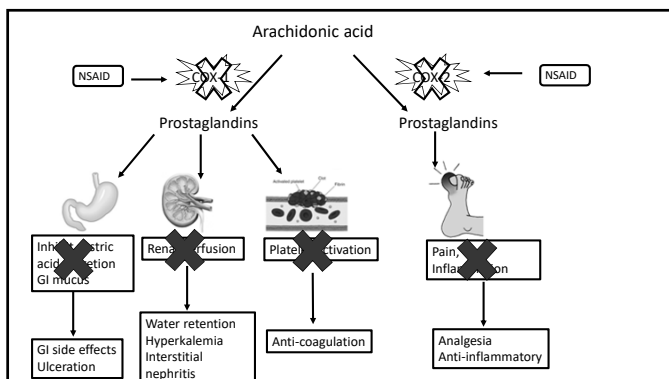
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NSAIDs

- **Bleeding**
 - COX-1 vs COX-2
- **Renally Cleared**
 - Lithium
 - Which NSAIDs are safest?
 - Methotrexate
 - ACE inhibitors/Diuretics

McGill MR, Jaschke H. Metabolism and disposition of acetaminophen: recent advances in relation to hepatotoxicity and diagnosis. Pharm Res. 2013;30(9):2174-87.
Zhang Q, Bai Q, Solter C, Drouot L, Simonneau G, Alvarez JC, Puvion S, et al. Interaction between acetaminophen and warfarin in adults receiving long-term oral anticoagulants: a randomized controlled trial. Eur J Clin Pharmacol. 2015;47(3):309-14.
Saso-Tenkorsmaa J, Fudin J. Drug Interactions in Cancer Patients Requiring Concomitant Chemotherapy and Analgesics. Practical Pain Management. 2013 May; 13 (6):50-64.

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Skeletal Muscle Relaxants

- **CNS Depressants**
- **Tizanidine**
 - CYP1A2 inhibitors – increased exposure
 - Ciprofloxacin
 - Birth Control
 - Verapamil
- **Cyclobenzaprine**
 - Cardiac toxicity

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Antidepressants

SNRIs

- Duloxetine
 - CYP2D6 and CYP1A2
- Venlafaxine
 - CYP3A4

SSRIs

- CYP2D6
- Fluvoxamine – CYP1A2

Bupropion

- CYP2B6

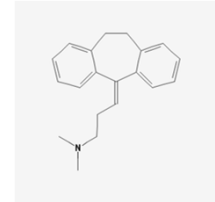
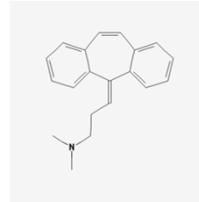
Medication	CYP activity
Duloxetine	2D6 inhibitor (weak) PGP inhibitor
Venlafaxine	2D6 inhibitor (weak)
Desvenlafaxine	2D6 inhibitor (weak)
Bupropion	2D6 inhibitor (strong)

Tricyclic Antidepressants (TCAs)

Cardiotoxic medications
cyclobenzaprine

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Cyclobenzaprine vs Amitriptyline



<https://pubchem.ncbi.nlm.nih.gov>

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Case Assessment

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Case: JB

- JB is a 45 year old Caucasian male who has a history of cervical stenosis at C5-6 with myelopathy. He has been on tramadol for a number of years but he comes to you for assistance with optimal control of neuropathic pain. You initiate Carbamazepine 100mg PO Daily x 7 days then 200mg PO Daily.
- Three weeks later JB calls the clinic in distress and he reports being in the worst pain he has experienced in years.
- Why is JB suddenly in pain?

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Case: KK

KK is a 69 year old African American male with chronic low back pain s/p laminectomy.

Current Medications:

Acetaminophen 1000mg PO TID	Docusate/Senna 4 tablets PO QHS
Methadone 5mg PO QID	Celecoxib 100mg PO BID
Dabigatran 150mg PO BID	Omeprazole 20mg PO QAM
Metoprolol Tartrate 50mg PO BID	Venlafaxine 100mg PO BID
Lisinopril 10mg PO daily	Metformin 500mg PO TID
Atorvastatin 40mg PO daily	

What drug-drug interactions are you concerned about?

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Case: KK

KK reports to the ED with complaints of productive cough x 1 week with bright green sputum and is diagnosed with community acquired pneumonia. Which of the following drug or drugs do you want to avoid and why?

Discussion

Amoxicillin/Clavulanic acid
Cefdinir
Sulfamethoxazole/Trimethoprim
Levofloxacin

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Conclusions / Summary

- Considering drug-drug interactions is key in selecting the safest and most efficacious therapies
- Understanding the pharmacology is essential to appropriately identify drug-drug interactions
- Pharmacogenetic differences among patients can highly impact efficacy, drug interactions, and ability to tolerate medications.