Demystifying Drug Interactions with Combined Analgesics Across Various Therapeutic Classes

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The overarching goal of PCSS-O is to offer evidence-based trainings on the safe and effective prescribing of opioid medications in the treatment of pain and/or opioid addiction.

Our focus is to reach providers and/or providers-in-training from diverse healthcare professions including physicians, nurses, dentists, physician assistants, pharmacists, and program administrators.
Educational Objectives

• At the conclusion of this activity, participants should be able to:
  1. Classify cytochrome P450 (CYP450) system nomenclature and describe role of CYP450 and p-glycoprotein in pharmacokinetics
  2. Recognize key CYP450 mediated drug-drug interactions
  3. Identify potential drug-drug interactions and important considerations when prescribing various analgesic classes and adjuvants
Common Mechanisms for Drug-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

- CYP450 induction, inhibition, autoinduction, substrates
  - Carbamazepine/methadone, codeine or tramadol/sertraline

- P-glycoprotein
  - Morphine/rifampin, methadone/telaprevir
Adverse Outcomes Due to Drug-Drug Interactions in Stable Patients

- Often occur after the addition of a new drug that increases or decreases the effect of a drug a patient is already taking.
- Time course varies depending on the pharmacokinetics of the drugs involved:
  - Most adverse outcomes manifest themselves within the first week or two of starting therapy with a new drug.
  - Adverse outcomes can also occur in patients who have been stabilized on interacting drugs for weeks or months.

Adverse Outcomes Due to Drug-Drug Interactions in Stable Patients

• Pharmacodynamic DDIs
  ▪ Risk may continue as long as a patient receives the 2 drugs; eg, increased risk of bleeding when SSRIs are given with warfarin

• Addition of third drug
  ▪ Sometimes a patient is on long-term therapy with 2 interacting drugs with no adverse outcomes, but a reaction occurs when a third drug is added

• Stopping a drug
  ▪ If a drug is titrated to effect in the presence of an inhibitor or inducer, when the inhibitor or inducer is stopped, the drug concentrations may become subtherapeutic or excessive

• Change in renal function
  ▪ Some DDIs are more likely to result in adverse outcomes in patients with impaired renal function

Cytochrome P450 Review
CYP450 Nomenclature

• Cytochrome is designated CYP
• CYP (#) - # identifying the enzyme family
• CYP (#) (A,C) - subfamily designation
• CYP (#) (A,C) (#) - individual enzyme (based on when enzyme was discovered)

• Examples:
  - CYP3A4
  - CYP2D6
  - CYP1A2
Cytochrome P450 Enzyme Tree

Terminology

- **Inducer**
  - 3 weeks
- **Inhibitor**
  - 48 hours
- **Substrate**
- **Genetic polymorphism**
  - Poor metabolizer
  - Intermediate metabolizer
  - Extensive metabolizer*
  - Ultrarapid metabolizer
- **Autoinducer**
  - Carbamazepine
Warfarin Metabolism by CYP2C9

Free warfarin in blood, INR=2.5

Liver/Gut Metabolism

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Rifampin Induces CYP2C9 Metabolism of Warfarin

Amiodarone Inhibits CYP2C9 Metabolism of Warfarin

Amiodarone is a CYP2C9 inhibitor discouraging CYP2C9 production.

More free warfarin in blood due to less metabolism from amiodarone inhibition of CYP2C9, INR = 4.8.

Paroxetine Inhibits CYP2D6 Conversion of the Prodrug Codeine to Morphine

Paroxetine inhibits production of 2D6 enzymes which precludes the conversion of codeine to morphine.

Codeine only is available now due to inhibited production of 2D6, no morphine and minimal analgesia.
p-Glycoprotein (pGP) Efflux Pumps

- pGP efflux pumps “pump” drugs (pGP substrates) back into the gut
  - Decreases movement of some drugs across biological barriers, which decreases the amount of drug available in the blood
- pGP pumps located in the liver, gut wall, brain, and kidney

**pGP inducer**
Causes creation of more pGP: blood drug levels go down. pGP inducers also reduce amount of some toxin ingestion, by pumping them back into the gut.

**pGP inhibitor**
Inhibits the drug-pump-inhibitor and, consequently, blood drug levels increase.

Polling Question

Drug A is a substrate of enzyme X. Drug B is an inducer of enzyme X. A patient has been using Drug A with good results. The patient has now started therapy with Drug B. What will happen to the concentration of Drug A?

a) Increase  
b) Decrease  
c) Stay the same  
d) Not enough information is given  
e) None of the above
Polling Question

Drug A is a substrate of enzyme X. Drug B is an inhibitor of enzyme X. A patient has been using Drug A with good results. The patient has now started therapy with Drug B. What will happen to the concentration of Drug A?

a) Increase  
b) Decrease  
c) Stay the same  
d) Not enough information is given  
e) None of the above
Opioid Pharmacokinetics and Drug-Drug Interactions
Shown in red are the major CYP450 enzymes involved in phase I metabolism; patterns of drug metabolites may reflect the metabolic profile of the patient. Actual proportions of individual metabolites will vary.

Pharmacogenetics testing is available for CYP2D6

Phase II reactions (eg, glucuronide conjugation) are not shown but are prominent for most compounds.
## Medication Metabolism

<table>
<thead>
<tr>
<th>Phase of metabolism</th>
<th>Key enzymes involved</th>
<th>Examples of opioid medication metabolized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>CYP450</td>
<td>Codeine, hydrocodone, oxycodone, tramadol, fentanyl, methadone, buprenorphine</td>
</tr>
<tr>
<td></td>
<td>CYP2D6, CYP2C19, CYP2B6, CYP2C9, CYP3A4, and CYP3A5</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>Uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT)</td>
<td>Morphine, oxymorphone, hydromorphone, tapentadol, levorphanol</td>
</tr>
<tr>
<td></td>
<td>UGT2B7 and UGT2B15</td>
<td></td>
</tr>
</tbody>
</table>
Tramadol Metabolism

- 6,000 X weaker binding affinity to mu opioid receptors compared to morphine
- Serotonin and norepinephrine activity

Tramadol

- CYP2B6
- CYP3A4

N-desmethyltramadol (M2) (inactive)

- CYP2B6
- CYP3A4

O-desmethyltramadol (M1) (active)

- CYP2D6

N,O-didesmethyl tramadol (M5)

- CYP2B6
- CYP3A4

O-desmethyl tramadol glucuronide (M5)

- UGT2B7
- UGT1AB

N,N-didesmethyl tramadol (M3)

# Common CYP3A4 Inhibitors and Inducers

<table>
<thead>
<tr>
<th>CYP3A4 Inhibitors</th>
<th>CYP3A4 Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant</td>
<td>Armodafinil</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Griseofulvin</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Bicalutamide</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Carbamazepine*</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Primidone</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Etravirine</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Rifabutin</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Fosamprenavir</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Fosphenytoin</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>St. John’s Wort</td>
</tr>
</tbody>
</table>

Polling Question

Oxycodone is metabolized by CYP3A4. A patient has been using oxycodone with good results. The patient has now started therapy with clarithromycin, which is a CYP3A4 inhibitor. What is the likely result?

a) The patient could suffer fatal respiratory depression
b) The patient experiences a subtherapeutic analgesic response
c) Not enough information is given
CASE: JB

• 45-year-old Caucasian male
  ▪ History of cervical stenosis at C5-6 with myelopathy
  ▪ Has been on tramadol for a number of years, but comes to you for assistance with optimal control of neuropathic pain
  ▪ You initiate carbamazepine 100 mg PO daily x 7 days, then 200 mg PO daily

• 3 weeks later: JB calls the clinic in distress
  ▪ Reports being in the worst pain he has experienced in years

• Why is JB suddenly in pain?
JB has been on tramadol for several years. Tramadol is metabolized by CYP3A4 and CYP2B6 to the inactive metabolite and by CYP2D6 to the active metabolite.

You add carbamazepine to treat JB’s neuropathic pain. What is the likely cause of JB’s sudden pain?

a) Carbamazepine is a CYP3A4 inducer. It increases metabolism of tramadol by CYP3A4 to an inactive metabolite

b) Carbamazepine is a CYP2D6 inducer. It increases metabolism of tramadol by CYP2D6 to an active metabolite

c) Not enough information is given
### Common CYP2D6 Inhibitors

<table>
<thead>
<tr>
<th>CYP2D6 Inhibitors</th>
<th>CYP2D6 Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Terbinafine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Thioridazone</td>
</tr>
</tbody>
</table>

- There are no known CYP2D6 inducers
- Genetics, rather than drug therapy, accounts for most ultrarapid CYP2D6 metabolizers

Methadone Metabolism

R: Responsible for analgesia

R-methadone (parent drug) → CYP3A4 → EDDP (inactive metabolite)

S: Sorrowing outcome (cardiotoxic effects, QT prolongation with potential of Torsade de pointes)

S-methadone (parent drug) → CYP2B6 → EDDP (inactive metabolite)

CYP2B6 selectively metabolizes S-enantiomer
Potential risk?

QTc Prolonging Drugs

Methadone

Quinolone antibiotics

Macrolide antibiotics

Buprenorphine

Amiodarone/Sotalol

Sertraline/Citalopram

Quetiapine

Venlafaxine

Ondansetron

Fluconazole/Ketoconazole

QTc Prolonging Drugs: Buprenorphine

- **Buprenorphine buccal film**
  - 900 mcg Q12H (maximum dose)
    - QTc 450-480 msec for 2% of patients
  - Up to 9.2 msec QT prolongation

- **Buprenorphine transdermal patch**
  - 20 mcg/hour (maximum dose)
  - No QTc prolongation seen in trials at this dose

**QT Prolongation of Various Medications**

- Thioridazine 300 mg/d
- Ziprasidone 160 mg/d
- Quetiapine 750 mg/d
- Moxifloxacin 400 mg
- Risperidone 16 mg/d
- Citalopram
- Buprenorphine transdermal patch 40 mcg/hr
- Escitalopram
- Olanzapine 20 mg/d
- Antidepressants (SSRI vs TCA)
- Buccal buprenorphine 3 mg/naltrexone 50 mg
- Haloperidol 15 mg/d

**Note, these data are:**

- Not meant for direct comparisons between the various agents because of differences in study design, QT correction strategies, and population variations
- Provided as context for the current landscape of QT-prolonging drugs

# Methadone vs Levorphanol

<table>
<thead>
<tr>
<th>Methadone</th>
<th>Both</th>
<th>Levorphanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; kappa opioid agonist</td>
<td>&gt; kappa opioid agonist</td>
<td></td>
</tr>
<tr>
<td>Serotonin reuptake inhibitor</td>
<td>Delta opioid agonist</td>
<td></td>
</tr>
<tr>
<td>CYP450 metabolism</td>
<td>Mu opioid agonist</td>
<td>Phase II glucuronidation</td>
</tr>
<tr>
<td>pGP substrate</td>
<td>NMDA antagonist</td>
<td>Not a known pGP substrate</td>
</tr>
<tr>
<td>( t_{1/2} = 15-60 ) hours</td>
<td>Norepinephrine reuptake inhibitor</td>
<td>( t_{1/2} = 11-16 ) hours</td>
</tr>
<tr>
<td>Up to 150 hours in polymorphic outliers</td>
<td></td>
<td>No QTc prolongation</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacogenetics

- Drug metabolism and variability among patients in terms of drug response can sometimes be explained by genetic variations within CYP450 enzymes
  - 2 patients: same gender, weight, height, and race on oxycodone ER 10 mg Q12H
    - Patient A’s serum oxymorphone level: as expected
    - Patient B’s serum oxymorphone level: elevated
  - Patients A and B are genetically tested:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Predicted phenotype</th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4/3A5</td>
<td>Normal metabolizer</td>
<td>Normal metabolizer</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Normal metabolizer</td>
<td>Normal metabolizer</td>
<td>Ultrarapid metabolizer</td>
</tr>
</tbody>
</table>

The Perfect Storm: Opioid Risks and “The Holy Trinity”

- Opioids, benzodiazepines, and carisoprodol have overlapping side effects
  - Drowsiness, respiratory depression (opioid), confusion, tremor, and seizures risk
- Combined, these drugs are synergistic in causing respiratory depression
  - Could collectively result in death

Non-Opioid Drug-Drug Interactions
Acetaminophen

• Metabolism
  ▪ Pediatrics: sulfation
  ▪ Adults: glucuronidation
  ▪ CYP2E1: conversion to N-acetyl-p-benzoquinone imine (NAPQI)
    ‒ Hepatotoxic metabolite

• Drug-drug interactions
  ▪ Avoid concomitant hepatotoxic therapies
  ▪ Imatinib, dasatinib, and sunitinib inhibit glucuronidation
    ‒ Max acetaminophen dose: 1,300 mg/day
  ▪ Warfarin
    ‒ Possibly: CYP2C9, NAPQI, and/or hepatotoxicity
    ‒ Increased anticoagulant effect: INR ↑

NSAIDs

• Bleeding
  - COX-1 vs COX-2

• Renally cleared
  - Lithium
    - Which NSAIDs are safest?
  - Methotrexate
  - ACE inhibitors/diuretics
Arachidonic acid

Inhibit gastric acid secretion
GI mucus

Prostaglandins

Renal perfusion

GI side effects
Ulceration

COX-1

COX-2

Water retention
Hyperkalemia
Interstitial nephritis

Anti-coagulation

Analgesia
Anti-inflammatory

Platelet activation

Pain, inflammation

NSAID

Anti-inflammation

Dr F
Skeletal Muscle Relaxants

- CNS depressants
- Tizanidine
  - CYP1A2 inhibitors – increased exposure
    - Ciprofloxacin
    - Birth control
    - Verapamil
- Cyclobenzaprine
  - Cardiac toxicity
Antidepressants

- **SNRIs**
  - Duloxetine
    - CYP2D6 and CYP1A2
  - Venlafaxine
    - CYP3A4
- **SSRIs**
  - CYP2D6
  - Fluvoxamine
    - CYP1A2
- **Bupropion**
- **Tricyclic antidepressants**
  - Cardiotoxic medications
  - Cyclobenzaprine

<table>
<thead>
<tr>
<th>Medication</th>
<th>CYP activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>2D6 inhibitor (weak) pGP inhibitor</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>2D6 inhibitor (weak)</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>2D6 inhibitor (weak)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>2D6 inhibitor (strong)</td>
</tr>
</tbody>
</table>

Cyclobenzaprine vs Amitriptyline

Case Assessment
CASE: MK

- 69-year-old African American male
  - Chronic low back pain s/p laminectomy

- Current medications:
  - Acetaminophen 1000 mg PO TID
  - Methadone 5 mg PO QID
  - Dabigatran 150 mg PO BID
  - Metoprolol tartrate 50 mg PO BID
  - Lisinopril 10 mg PO daily
  - Atorvastatin 40 mg PO daily
  - Docusate/senna 4 tabs PO QHS
  - Celecoxib 100mg PO BID
  - Omeprazole 20mg PO QAM
  - Venlafaxine 100mg PO BID
  - Metformin 500mg PO TID

- What drug-drug interactions are you concerned about?
CASE: MK

• MK reports to the ED with complaints of productive cough x 1 week with bright green sputum
  ▪ Diagnosed with community-acquired pneumonia

• Which of the following drug or drugs do you want to avoid and why?
  ▪ Amoxicillin/clavulanic acid
  ▪ Cefdinir
  ▪ Sulfamethoxazole/trimethoprim
  ▪ Levofloxacin
Conclusions

• Considering drug-drug interactions is key in selecting the safest and most efficacious therapies

• Understanding pharmacology is essential to appropriately identify drug-drug interactions

• Pharmacogenetic differences among patients can highly impact efficacy, drug interactions, and ability to tolerate medications


References


PCSS-O Colleague Support Program and Listserv

- PCSS-O Colleague Support Program is designed to offer general information to health professionals seeking guidance in their clinical practice in prescribing opioid medications.

- PCSS-O Mentors comprise a national network of trained providers with expertise in addiction medicine/psychiatry and pain management.

- Our mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.

- The mentoring program is available at no cost to providers.

For more information on requesting or becoming a mentor visit: [www.pcss-o.org/colleague-support](http://www.pcss-o.org/colleague-support)

- Listserv: A resource that provides an “Expert of the Month” who will answer questions about educational content that has been presented through PCSS-O project. To join email: pcss-o@aaap.org.
PCSS-O is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: Addiction Technology Transfer Center (ATTC), American Academy of Neurology (AAN), American Academy of Pain Medicine (AAPM), American Academy of Pediatrics (AAP), American College of Physicians (ACP), American Dental Association (ADA), American Medical Association (AMA), American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society for Pain Management Nursing (ASPMN), International Nurses Society on Addictions (IntNSA), and Southeast Consortium for Substance Abuse Training (SECSAT).

For more information visit: www.pcss-o.org
For questions email: pcss-o@aaap.org

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