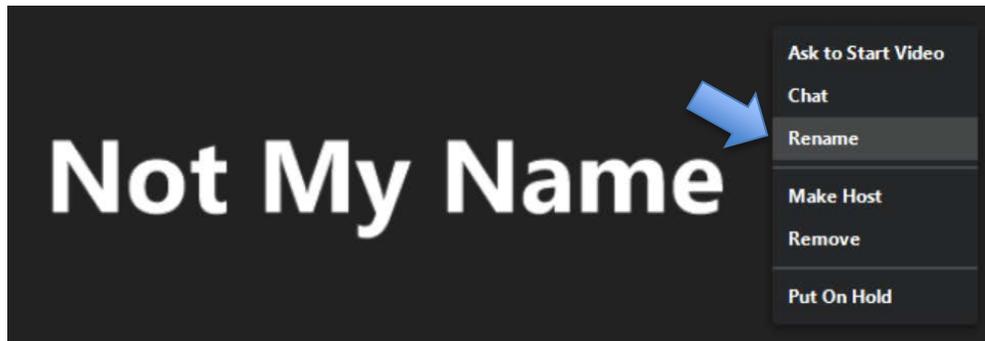




ECHO Idaho: Opioid Addiction and Treatment Clinic

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ECHO Idaho: Opioid Addiction and Treatment

Drug Interactions with Pain Medications

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The speaker has no significant financial conflicts of interest to disclose.

Learning Objectives

- Describe mechanisms for drug interactions
- Identify potential drug-drug interactions with opioids
- Recognize adverse reactions that may be caused by drug-drug interactions

Statistics on Adverse Effects/Drug Interactions

- The CDC estimates > 1 million individuals are seen in the ED each year for adverse drug reactions (ADR)
- A 2019 Rutgers study found that 38% of individuals discharged from the ED had at least 1 drug interaction identified

<https://www.statnews.com>, www.sciencedaily.com, <https://www.cdc.gov/>

Drug Interactions

- Polypharmacy increases the risk of drug-drug interactions
- A study demonstrated an overall prevalence of potential drug-drug interactions to be 27% among patients on long-term opioids
- Drug-drug interactions involving the cytochrome P450 system are common
- Other drug interactions involve overlapping toxicities

Cytochrome P450 System

- Enzymes that metabolize various drugs
- Of the many P450 enzymes, six are clinically relevant
 - CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5
- Drugs are substrates, inhibitors and/or inducers of the P450 system enzymes

2D6/3A4 Inhibitors & 3A4 Inducers

(not all inclusive)

- 2D6 Inhibitors

- SSRIs/SNRIs
- Bupropion
- Quinidine
- Amiodarone

- 3A4 Inducers

- Rifampin
- Carbamazepine
- Phenobarbital
- Phenytoin
- St. John's Wort

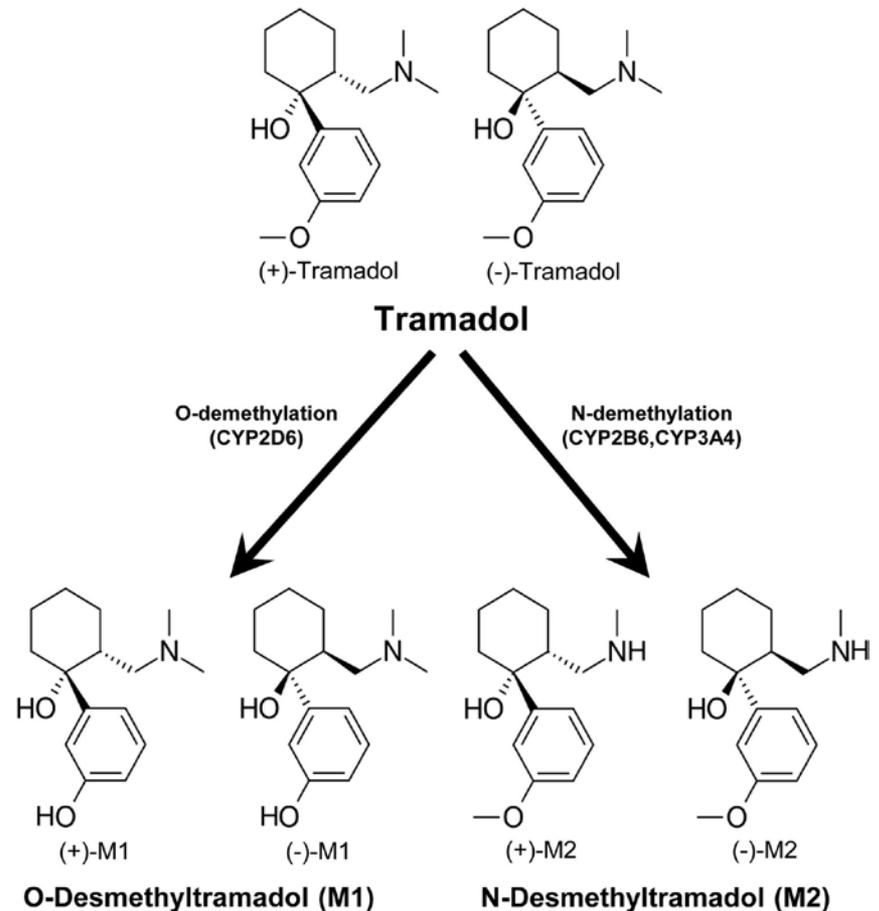
- 3A4 Inhibitors

- Erythromycin
- Clarithromycin
- Azole antifungals
- Protease inhibitors
- Verapamil
- Diltiazem

<https://drug-interactions.medicine.iu.edu/Main-Table.aspx>

Tramadol

- Metabolized by CYP450 enzymes 3A4 and 2D6
- Black box warning:
 - Concomitant use or discontinuation of 3A4 inducers, 3A4 inhibitors or 2D6 inhibitors with tramadol are complex due to the effects on the parent drug, tramadol and the active metabolite, M1
 - 2D6 inhibitors leads to lower concentrations of the active metabolite (M1) and typically reduced analgesia
 - 3A4 inducers decrease efficacy
 - Monitor for opioid withdrawal
 - Monitor for toxicity when 3A4 inducer discontinued



Tramadol: 2D6 Polymorphism

Poor metabolizers

- Tramadol is poorly metabolized to its active metabolite
- Drug-drug interactions with 2D6 inhibitors variable
- Recommend selecting a different pain medication

Ultra-rapid metabolizers

- Convert tramadol to its active metabolites more rapidly and to a greater extent
 - ↑ concentrations of M1 (active metabolite)
- Concern for life threatening respiratory depression
- Do not use in < 18 years

Tramadol Drug Interactions: Additive Toxicities

- **Respiratory depression & sedation**

**Monitor for sedation; use with caution in COPD, sleep apnea, heart failure and obesity*

- Benzodiazepines
- Opioids

- **Increased risk of seizures**

- Antipsychotics
- Bupropion
- SSRIs/SNRIs
- MAOIs
- Opioids
- Tricyclic antidepressants

- **Serotonin syndrome**

**Monitor for mental status changes, tachycardia, hyperthermia, hyperreflexia, incoordination, GI*

- Antipsychotics
- SSRIs/SNRIs
- Linezolid
- Lithium
- MAOIs
- Tricyclic antidepressants
- Triptans
- St. John's Wort
- 2D6/3A4 inhibitors

Methadone: Drug Interactions

- Metabolized by CYP450 enzymes **3A4, 2D6, 2B6, 2C9** and **2C19**
 - Inhibitors: increased toxicities due to increased concentrations
 - Azole antifungals, clarithromycin, protease inhibitors
 - SSRIs/SNRIs, bupropion, amitriptyline, quinidine
 - Inducers: reduced concentrations of methadone
- *Fatal overdoses have occurred with D/C of P450 inducers
 - May induce withdrawal s/s
 - Rifampin, phenobarbital, phenytoin, St. John's Wort

Methadone: Overlapping Toxicities

- **Respiratory depression**

*Peak respiratory depressant effect occurs later/lasts longer than peak analgesic effect

- Benzodiazepines
- Opioids
- CNS depressants

- **Serotonin Syndrome**

- Antipsychotics
- SSRIs/SNRIs
- Linezolid
- Lithium
- MAOIs
- Tricyclic antidepressants
- Triptans
- St. John's Wort
- 2D6/3A4 inhibitors

- **CNS depression**

- Alcohol
- CNS acting meds

- **QT prolongation**

**Monitor QT interval and arrhythmias (Risk factors include older age, female, ↓ K, ↓ Mg, bradycardia, diuretic use)*

- SSRIs, TCAs, antipsychotics
- Macrolides, moxifloxacin, azole antifungals
- Amiodarone, flecainide, quinidine

Opioids: Metabolism

Phase 1

- Drugs
 - Codeine
 - Hydrocodone
 - Oxycodone
 - Fentanyl
- P450 mediated
- *Increased potential for drug interactions*

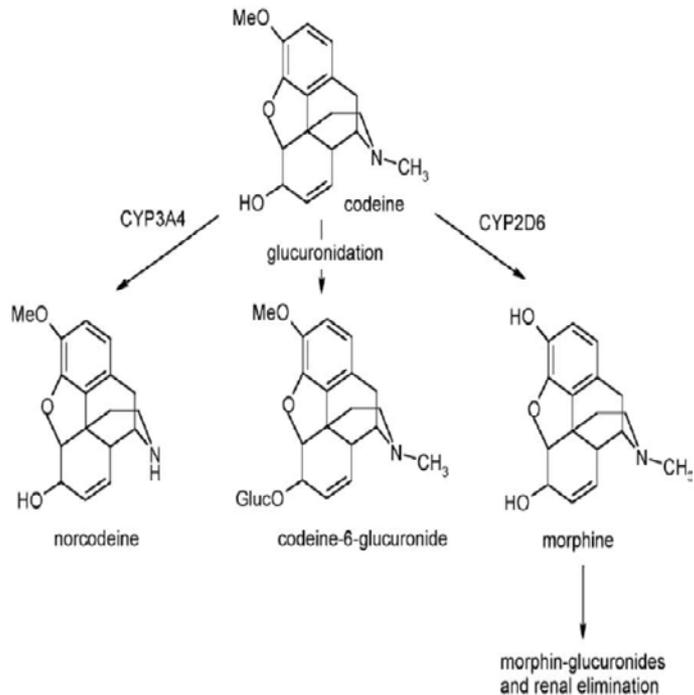
Phase 2

- Drugs
 - Morphine
 - Oxymorphone
 - Hydromorphone
- *Less potential for drug interactions*

Opioids: Codeine, Hydrocodone, Oxycodone, Fentanyl

- Metabolized via 3A4 and 2D6
- Overlapping toxicities
 - **Respiratory depression**
 - *Monitor for sedation; use with caution in COPD, sleep apnea, heart failure and obesity*
 - Benzodiazepines
 - Other CNS depressants
 - **Seizures**
 - When used with other meds that lower seizure threshold
 - **Serotonin syndrome**
 - SSRIs/SNRIs, TCAs, MAOIs, bupropion, mirtazapine, triptans, antiemetics (ondansetron/Zofran, dolasetron/Anzemet)

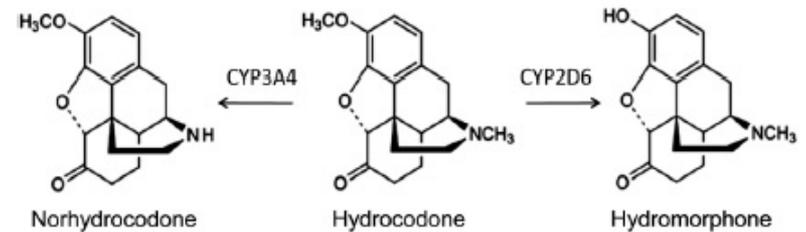
Codeine



- Metabolized via 3A4 (inactive metabolites) and 2D6 (active metabolites)
- Inhibitors of 2D6, reduce analgesic activity
- 3A4 inhibitors enhance conversion to morphine and in ultra-metabolizers, may result in toxic morphine concentrations

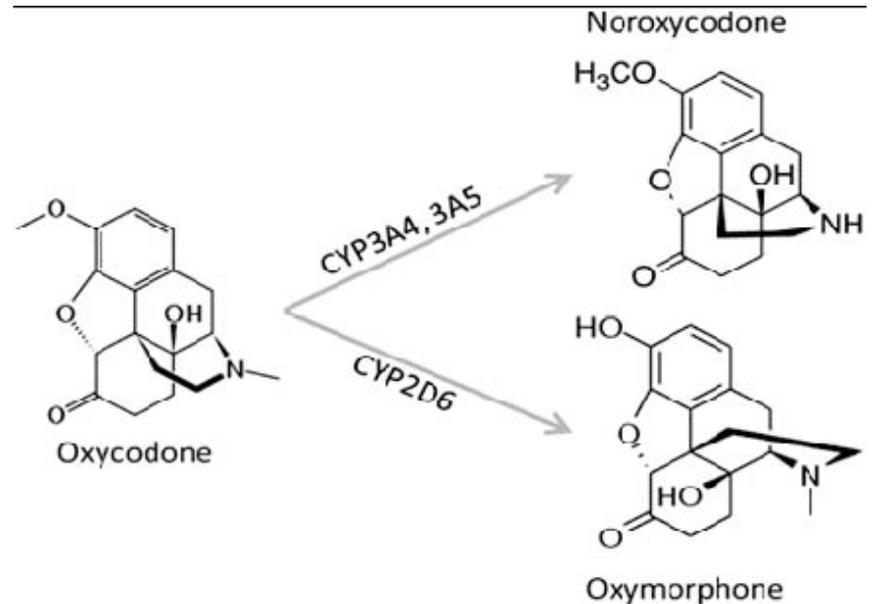
Hydrocodone

- Metabolized via 2D6 to hydromorphone (active)
- 2D6 inhibitors reduce conversion to hydromorphone
 - resulting in less analgesia



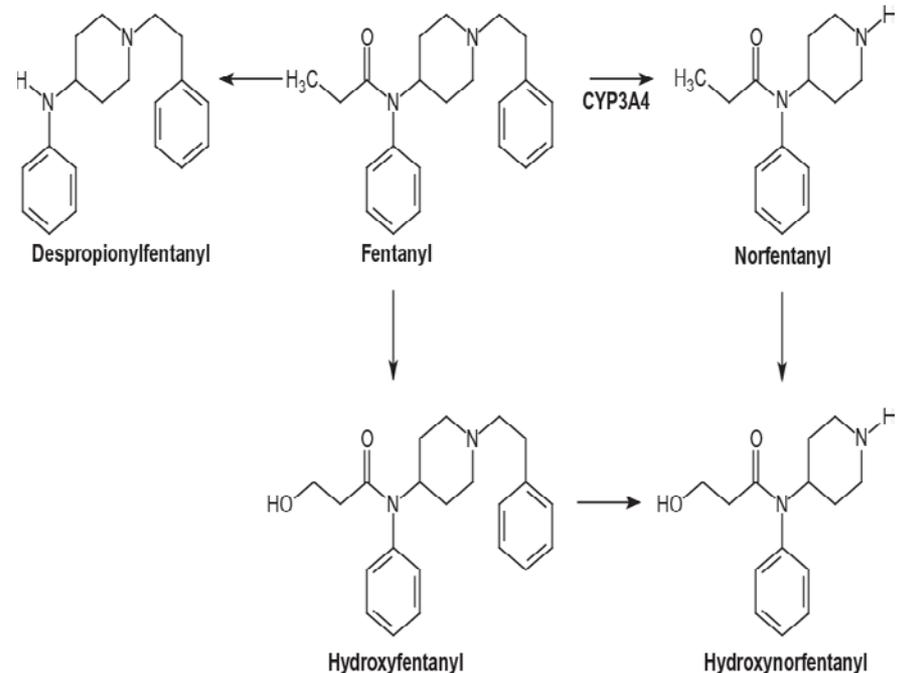
Oxycodone

- Metabolized primarily by 3A4
 - 2D6 minor pathway (~10%)
- 3A4 inhibitors result in increased opioid effects
 - Black box warning due to respiratory depression
 - Clarithromycin, azoles, protease inhibitors, grapefruit juice
- 3A4 inducers reduce opioid effects
 - Rifampin
 - St. John's Wort



Fentanyl

- Metabolized by 3A4
- 3A4 inhibitors result in increased opioid effects
 - Black box warning due to respiratory depression and increased/prolonged adverse reactions
 - Clarithromycin, azoles, protease inhibitors, grapefruit juice
- 3A4 inducers reduce opioid effects
 - Rifampin
 - St. John's Wort
 - Monitor for enhanced toxicity when discontinued



Key Points

- Many drug-drug interactions exist among opioids
- Life threatening adverse effects may occur
- Drug-drug interactions should be evaluated prior to adding the opioids or other agents to an opioid

Drug Interaction Tools

- Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007).
<https://drug-interactions.medicine.iu.edu>
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- LexiComp
- Pharmacist's Letter



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