Welcome! The session will start at 12:15pm MT.

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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 Rutger’s study found that 38% of individuals discharged from the ED had at least 1 drug interaction identified

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


• https://www.drugs.com/drug_interactions.html
References

• https://www.statnews.com/pharmalot/2016/11/22/side-effects-emergency-room/
• https://www.cdc.gov/medicationsafety/adult_adversedrugevents.html
• LexiComp
• Pharmacist’s Letter
ECHO Idaho: Opioid Addiction and Treatment

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