Methadone and Buprenorphine-Associated Drug-Drug Interactions

Andrew J. Saxon, M.D.

With acknowledgements to Elinore F. McCance-Katz, MD, PhD
Andrew J. Saxon, M.D.,
Disclosures

- Andrew Saxon, MD, was a member of Alkermes’ advisory board within the past 12 months.

The content of this activity may include discussion of off label or investigative drug uses. The faculty is aware that it is their responsibility to disclose this information.
The overarching goal of PCSS is to train a diverse range of healthcare professionals in the safe and effective prescribing of opioid medications for the treatment of pain, as well as the treatment of substance use disorders, particularly opioid use disorders, with medication-assisted treatments.
Educational Objectives

At the conclusion of this activity participants should be able to:

• Compare epidemiologic data on drug-drug interactions between opioids and other medications

• Review possible explanations for increases in drug-drug interactions

• Describe physiological and pharmacokinetic basis for adverse drug interactions

• Identify strategies for reducing risk
Adverse Drug Interactions

- Accidental deaths are the leading cause of death in those aged 1-44 with highest rates in 25-44 y.o.

- Poisoning is now leading cause of accidental deaths; >300% increase in poisoning deaths 1999-2016; opioids most frequently named drug in poisonings

Adverse Drug Interactions

Adverse drug interactions involving opioids:

• Overdose
• Combining medications
  ▪ E.g.: heroin or methadone or buprenorphine or opioid analgesics:
    ○ With other prescribed medications
    ○ With illicit substances
    ○ With alcohol
Based on data available for analysis on: 11/4/2018

Select Jurisdiction
United States

Figure 2. 12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class: United States

NOTES: Reported provisional counts for 12-month ending periods are the number of deaths received and processed for the 12-month period ending in the month indicated. Provisional counts may not include all deaths that occurred during a given time period. Therefore, they should not be considered comparable with final data and are subject to change. Predicted provisional counts represent estimates of the number of deaths adjusted for incomplete reporting (see Technical notes).

Deaths are classified by the reporting jurisdiction in which the death occurred. Jurisdictions are selected for inclusion in this dashboard based on three measures of data quality: (a) overall completeness of reporting (≥ 90%), (b) the percentage of records pending investigation (≤ 1%), and (c) the percentage of overdose deaths with drug specified (≥ 90%). Drug overdose deaths are identified using ICD–10 underlying cause-of-death codes: X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by ICD–10 multiple cause-of-death (MCOD) codes: heroin, T40.1; natural and semisynthetic opioids, including drugs such as oxycodone, hydrocodone, and morphine, T40.2; methadone, T40.3; synthetic opioids, including drugs such as fentanyl and tramadol and excluding methadone, T40.4; cocaine, T40.5; and psychoactive substances with abuse potential, including drugs such as methamphetamine, T43.6. Opioid overdose deaths are identified by the presence of any of the following MCOD codes: opium, T40.0; heroin, T40.1; natural and semisynthetic opioids T40.2; methadone, T40.3; synthetic opioids, T40.4; or other and unspecified narcotics, T40.6. Categories are not mutually exclusive because deaths may involve more than one drug. Among deaths with an underlying cause of drug overdose, the percentage with at least one drug or drug class specified was determined using MCOD codes in the range of T38–T50.8.
# Methadone-Associated Adverse Effects

## Drugs Mentioned with Methadone
- methadone only (38%)
- alcohol
- alprazolam
- carisoprodol
- clonazepam
- cocaine
- duloxetine, amitriptyline
- fluoxetine, trazodone
- heroin
- hydrocodone
- marijuana
- MDMA (ecstasy)
- methamphetamine
- morphine
- narcotic analgesics
- olanzapine
- oxycodone
- quetiapine
- unspecified benzodiazepines
- zolpidem

## RADARS DEATHS (2003-2008)
- methadone only (33%)
- alcohol (7%)
- amitriptyline (8%)
- atypical antipsychotics (9%)
- benzodiazepines (52%)
- cocaine (7%)
- hydrocodone (7%)
- other anticonvulsant (7%)
- other narcotic (8%)
- SSRIs (8%)

Maxwell and McCance-Katz, 2010
# Buprenorphine-Associated Adverse Effects

**DAWN ED-2007, Buprenorphine+Naloxone**

- buprenorphine+naloxone only (40%)
- alcohol
- alprazolam
- bupropion
- carisoprodol
- clonazepam
- clonidine
- cocaine
- cyclobenzaprine
- fentanyl
- heroin
- hydrocodone
- hydromorphone
- lithium
- lorazepam
- marijuana
- methadone
- modafinil
- other benzodiazepines
- oxycodone
- paroxetine
- quetiapine
- risperidone
- sertaline
- trazodone
- zolpidem

**DAWN ED-2007, Buprenorphine Only**

- methadone only (33%)
- alcohol (7%)
- amitriptyline (8%)
- atypical antipsychotics (9%)
- benzodiazepines (52%)
- cocaine (7%)
- hydrocodone (7%)
- other anticonvulsant (7%)
- other narcotic (8%)
- SSRIs (8%)

Maxwell and McCance-Katz, 2010
Underlying Reasons for Drug-Drug Interactions

- Legacy patients continue to receive opioid analgesics for pain
- Many with pain have co-occurring medical and/or mental disorders
- Patients believe prescribed drugs are ‘safe’
- Lack of patient education about adverse events that can occur
- May not understand need to take as prescribed
- Sharing/selling
Pathophysiology of Drug-Drug Interactions

- **Pharmacokinetic:**
  - what the body does to the drug (or not)

- **Pharmacodynamic:**
  - what the drug or drugs do to the body
Pharmacokinetic Interactions

- Drug (in presence of other drugs)
  - May be better absorbed; e.g.: slowed GI motility
  - Altered efflux (P-glycoprotein effects)

- Inhibition or induction of metabolism; CYP enzymes or glucuronidation effects

- Net increase in exposure to drug(s) or reduction to the point of inducing physical withdrawal

- E.g.:
  - Ciprofloxacin inhibition of methadone metabolism
  - Rifampin induction of buprenorphine metabolism

McCance-Katz et al., 2011, Rifampin effect on buprenorphine PK
Pharmacodynamic Interactions

- PK interactions may have associated pharmacodynamic consequences
- Pharmacodynamic interactions can occur in the absence of a PK interaction
- Two drugs with similar pharmacological characteristics interact synergistically
  - Increases potential toxicity of drug
- Opioids and benzodiazepines
  - E.g.: alprazolam with methadone
- Opioids and alcohol
Opioids and Other Drugs: Basis of Adverse Events

• Why are we seeing adverse events and deaths in methadone-using individuals who co-consume psychotropics: SSRIs, antipsychotics?

• Not formally studied, but…
  ▪ Methadone metabolized by CYP 3A4, 2D6, 2B6, 2C9/10
  ▪ Buprenorphine metabolized by mainly 3A4
  ▪ Some SSRIs and some antipsychotics can inhibit metabolic enzymes
  ▪ May lead to increased plasma concentrations of drugs and associated toxicities
  ▪ E.g.: fluoxetine and fluvoxamine: inhibit both 3A4 and 2D6
  ▪ Paroxetine, sertraline, citalopram, and escitalopram: inhibit CYP 2D6 only
Opioids and Other Drugs: Basis of Adverse Events

• Methadone linked to blockade of human ether a go go related gene (hERG) potassium channels that has been reported to increase risk for arrhythmia (Torsade de Pointes)

• As methadone concentrations rise; risk of adverse events increases
  - High dose (> 100 mg/d methadone)
  - Drug interactions that increase methadone exposure through inhibition of methadone metabolism
    o (e.g.: fluvoxamine/methadone interaction)
  - Drug interactions that occur when an inducing drug is given; methadone dose increased to maintain efficacy; then the drug is withdrawn and methadone dose is not concomitantly lowered
    o E.g.: lopinavir/ritonavir/methadone interaction
Avoiding Adverse Interactions

• Think about metabolic interactions

• Warn patients/families about toxicities: cognitive impairment, increased sedation, slowed, loud breathing

• If concomitant medications are needed, try to use medications less likely to impair opioid metabolism
  ▪ Methadone: venlafaxine, SSRIs excluding fluoxetine/fluvoxamine
  ▪ Buprenorphine: mainly 3A4 substrate; avoid fluoxetine/fluvoxamine

• Buprenorphine may be preferable to methadone in those needing other medications because there are fewer expected interactions, but there are few data to confirm this supposition
# Potential Methadone Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Class or Specific Drug</th>
<th>Interaction</th>
<th>Putative Mechanism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiretrovirals</strong></td>
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<tr>
<td>Efavirenz, Lopinavir, Nevirapine, Elvitegravir</td>
<td>Reduction in serum methadone levels</td>
<td>Induction of CYP 450 3A4; Induction of CYP 450 2C9/10 (Elvitegravir)</td>
<td>Clinically significant opioid withdrawal symptoms likely</td>
</tr>
<tr>
<td>Abacavir, Etravirine, Nelfinavir, Ritonavir, Squinavir, Tipranavir</td>
<td>May reduce serum methadone levels</td>
<td>Induction of CYP 450 3A4</td>
<td>Clinically pertinent opioid withdrawal symptoms usually not seen with these agents</td>
</tr>
<tr>
<td><strong>Didanosine, Stavudine</strong></td>
<td>Reduction in didanosine, stavudine plasma concentration</td>
<td>Decreased bioavailability</td>
<td>Possible decreased efficacy of didanosine, stavudine</td>
</tr>
<tr>
<td><strong>Zidovudine</strong></td>
<td>Increase in zidovudine plasma concentration</td>
<td>Unknown</td>
<td>Risk of zidovudine toxicity</td>
</tr>
<tr>
<td><strong>Delavirdine</strong></td>
<td>Increased methadone serum concentration</td>
<td>Inhibition of CYP 450 3A4</td>
<td>No clinically meaningful adverse events observed</td>
</tr>
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<tr>
<td>Antiretrovirals</td>
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<tr>
<td>Darunavir</td>
<td>Increased methadone serum concentration</td>
<td>Inhibition of CYP 450 3A4</td>
<td>Clinical impact uncertain. Monitor closely.</td>
</tr>
<tr>
<td>Rilpiravine, Maraviroc</td>
<td>Potential risk of Torsade de Pointes (cardiac arrhythmia)</td>
<td>QT Prolongation</td>
<td>Could be additive with methadone; monitor closely</td>
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<tr>
<td>Tricyclics: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine</td>
<td>Increases risk for constipation and sedation. Increases risk for QT prolongation and arrhythmia</td>
<td>Anticholinergic effects. Blockade of hERG channel.</td>
<td>Clinical experience with combination indicates it is generally safe with careful clinical monitoring.</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitors: citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline</td>
<td>May increase serum methadone levels. Increased risk for serotonin syndrome</td>
<td>Inhibition of CYP 450 3A4, 2D6. Blockade of serotonin transporter.</td>
<td>Clinical experience with combination indicates it is generally safe with careful clinical monitoring.</td>
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<tr>
<td>Monoamine oxidase inhibitors: Isocarboxazid, phenelzine, selegiline, tranylcypromine</td>
<td>Increased risk for serotonin syndrome.</td>
<td>Inhibition of serotonin metabolism.</td>
<td>Use with extreme caution and careful clinical monitoring.</td>
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<tr>
<td>Serotonin/ norepinephrine reuptake inhibitors: Duloxetine, desvenlafaxine, venlafaxine</td>
<td>Increased risk for serotonin syndrome. Increases risk for QT prolongation and arrhythmia (venlafaxine)</td>
<td>Blockade of serotonin transporter. Blockade of hERG channel (venlafaxine).</td>
<td>Clinical experience with combination indicates it is generally safe with careful clinical monitoring.</td>
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<tr>
<td>Ciprofloxacin, clarithromycin, erythromycin, azithromycin</td>
<td>May increase methadone serum levels. Increases risk for QT prolongation and arrhythmia</td>
<td>Inhibition of CYP 450 3A4. Blockade of hERG channel</td>
<td>One case report of sedation (ciprofloxacin). Clinical monitoring required.</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td></td>
<td>Induction of CYP 450 3A4</td>
<td>Severe opioid withdrawal can occur. Will need increased methadone dose. Or switch antibiotics (e.g. rifabutine)</td>
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<td><strong>Antifungals</strong></td>
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<tr>
<td>Ketoconazole, fluconazole, voriconizole</td>
<td>May increase methadone serum levels.</td>
<td>Inhibition of CYP 450 3A4</td>
<td>Little evidence for important clinical effects</td>
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<td>Anticonvulsants</td>
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<td>Carbamazepine, phenytoin</td>
<td>Reduction in serum methadone levels</td>
<td>Induction of CYP 450 3A4</td>
<td>Severe opioid withdrawal can occur. Will need increased methadone dose.</td>
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<td>Antiarrhythmics</td>
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<tr>
<td>Procainamide, quinidine</td>
<td>Increases risk for QT prolongation and arrhythmia</td>
<td>Blockade of hERG channel</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>amiodarone</td>
<td>May increase methadone serum levels. Increases risk for QT prolongation and arrhythmia</td>
<td>Inhibition of CYP 450 3A4. Blockade of hERG channel</td>
<td>Careful clinical monitoring required</td>
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<tr>
<td>Benzodiazepines</td>
<td>Additive CNS and respiratory depressant effects</td>
<td>Increased GABA activity</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Additive CNS and respiratory depressant effects</td>
<td>Increased GABA activity</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>May increase methadone serum levels</td>
<td>Inhibition of CYP 450 2D6</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>May increase methadone serum levels</td>
<td>Inhibition of CYP 450 3A4</td>
<td>No evidence major clinical effect</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Precipitated opioid withdrawal</td>
<td>Displaces methadone from µ-opioid receptors</td>
<td>contraindicated</td>
</tr>
</tbody>
</table>
Potential Buprenorphine Drug-Drug Interactions

• The following interactions are notable (mechanisms similar to those for methadone):
  ▪ Delavirdine, Darunavir, **Atazanavir**
    - Atazanavir does **not** appear to increase methadone levels
  ▪ Rifampin
  ▪ Benzodiazepines
Potential Buprenorphine Drug-Drug Interactions

- Buprenorphine not as susceptible as methadone to drug-drug interactions
  - Tighter binding to receptor may make blood levels less important
  - Has an active metabolite, nor-buprenorphine
  - Partial agonist effect may mitigate some pharmacodynamic interactions and reduce risk from elevated blood levels
  - Does not prolong QT interval on ECG

- Many potential buprenorphine interactions have not been studied
Hep C  Direct Acting Antivirals

• Show no clinically meaningful interaction with methadone or buprenorphine
Strategies

• Training of prescribers:
  - Non-opioid strategies to effectively control pain
  - Safe prescribing
  - Avoid polypharmacy whenever possible

• Public outreach and education
  - E.g.: Important information about how medications interact including basic pharmacology of opioids
  - No medication sharing
  - How to safely dispose of medications - and this should be available at no charge to patients

• Use of Providers Clinical Support System
References


References

• Federation of State Medical Boards, 2004


References

PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.

- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medication-assisted treatment.

- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

- No cost.

For more information visit: http://www.pcssNOW.org/mentor
PCSS Discussion Forum

Have a clinical question?

Ask a Colleague
A simple and direct way to receive an answer related to medication-assisted treatment. Designed to provide a prompt response to simple practice-related questions.

Ask Now

http://pcss.invisionzone.com/register
**PCSS** is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

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Educate. Train. Mentor

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