Opioid-Associated Drug-Drug Interactions: What We Don’t Know is Hurting Us

Elinore F. McCance-Katz, MD, PhD
Medical Director, PCSS-O
Disclosures

• Grant Funding Provided by: NIDA/NIH, NIAAA/NIH, CSAT/SAMHSA
Learning Objectives

- Review of current epidemiologic data on drug-drug interactions between opioids and other medications
- Review possible explanations for increases in drug-drug interactions
- Review physiological and pharmacokinetic basis for adverse drug interactions
- 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; 145% increase in poisoning deaths 1999-2007; opioids most frequently named drug in poisonings
- 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
DAWN 2009

- Heroin 213,118 visits
- Narcotic Pain Relievers: 397,160 visits
- Oxycodone/combinations – 175,949 visits
- Hydrocodone/combinations – 104,490 visits
- Fentanyl/combinations – 22,143 visits
- Buprenorphine/combinations – 12,544 visits
- Alcohol involvement: 32% of visits

Source: Drug Abuse Warning Network, National Estimate, 2009
Opioid Abuse: Epidemiology

• Prevalence: Heroin
• 2009: 180,000 new users
• 900,000 addicted
• 0.7-0.9% (125,000) 8th, 10th, 12th graders endorse trying heroin at least once in the year prior to interview (2005-2009)
  – Monitoring the Future, 2010
Rates of Prescription Pain Medication Abuse

Nonmedical use of prescription pain medications (2009):

- Previous month misuse: 5.2 million over age 12
- 4.8% of those aged 18-25
- 1.9 million prescription narcotic users meet diagnostic criteria for opioid abuse or dependence (second only to marijuana (4.3 million))
- In 2006, deaths involving opioid analgesics was 1.63 times the number involving cocaine and 5.88 times the number involving heroin.

Source: NSDUH, 2006, 2010
Past Year Initiates for Specific Illicit Drugs Among Persons Aged 12 or Older: 2006

Numbers in Thousands

- Marijuana: 2,150
- Cocaine: 2,063
- Stimulants: 1,112
- Heroin: 977
- Sedatives: 860
- Pain Relievers: 845
- LSD: 783
- Inhalants: 267
- Ecstasy: 264
- Tranquilizers: 91
- PCP: 69
Source Where Pain Relievers Were Obtained for Most Recent Nonmedical Use among Past Year Users Aged 12 or Older: 2006

Source Where Respondent Obtained

- Bought/Took from Friend/Relative: 14.8%
- One Doctor: 80.7%
- Drug Dealer/Stranger: 3.9%
- More than One Doctor: 1.6%
- Bought on Internet: 0.1%
- Other: 4.9%

Source Where Friend/Relative Obtained

- One Doctor: 19.1%
- More than One Doctor: 3.3%
- Free from Friend/Relative: 55.7%
- Bought/Took from Friend/Relative: 14.8%
- Drug Dealer/Stranger: 1.6%
- Other: 2.2%

Note: Totals may not sum to 100% because of rounding or because suppressed estimates are not shown.

1 The Other category includes the sources: “Wrote Fake Prescription,” “Stole from Doctor’s Office/Clinic/Hospital/Pharmacy,” and “Some Other Way.”
Distribution of first-listed specified drugs among unintentional drug overdose deaths, US, 2005

- Methadone, 16.2%
- Other opioid painkillers, 22.0%
- Benzo./antidepress, 6.5%
- Cocaine, 25.1%
- Heroin, 7.7%
- Meth / amphet., 6.4%
- Other specified drugs, 16.1%
<table>
<thead>
<tr>
<th>Drugs Mentioned with Methadone</th>
<th>RADARS DEATHS (2003-2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methadone only (38%)</td>
<td>Methadone only (33%)</td>
</tr>
<tr>
<td>alcohol</td>
<td>alcohol (7%)</td>
</tr>
<tr>
<td>alprazolam</td>
<td>amitriptyline (8%)</td>
</tr>
<tr>
<td>carisoprodol</td>
<td>atypical antipsychotics (9%)</td>
</tr>
<tr>
<td>clonazepam</td>
<td>Benzodiazepines (52%)</td>
</tr>
<tr>
<td>cocaine</td>
<td>cocaine (7%)</td>
</tr>
<tr>
<td>Duloxetine, amitriptylene</td>
<td>hydrocodone (7%)</td>
</tr>
<tr>
<td>Fluoxetine, trazodone</td>
<td>other anticonvulsant (7%)</td>
</tr>
<tr>
<td>heroin</td>
<td>other narcotic (8%)</td>
</tr>
<tr>
<td>hydrocodone</td>
<td>SSRIs (8%)</td>
</tr>
<tr>
<td>marijuana</td>
<td></td>
</tr>
<tr>
<td>MDMA (ecstasy)</td>
<td></td>
</tr>
<tr>
<td>methamphetamine</td>
<td></td>
</tr>
<tr>
<td>morphine</td>
<td></td>
</tr>
<tr>
<td>narcotic analgesics</td>
<td></td>
</tr>
<tr>
<td>olanzapine</td>
<td></td>
</tr>
<tr>
<td>oxycodone</td>
<td></td>
</tr>
<tr>
<td>quetiapine</td>
<td></td>
</tr>
<tr>
<td>unspecified benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>zolpidem</td>
<td></td>
</tr>
</tbody>
</table>

**Methadone-Associated Adverse Effects**

From Maxwell and McCance-Katz, 2010
Buprenorphine-Associated Adverse Effects
From Maxwell and McCance-Katz, 2010
Medical Underpinnings of Adverse Events with Opioid Analgesics

- 1 in 4 Americans suffer from recurrent pain (day-long bout of pain/month)
- 1 in 10 Americans report having persistent pain of at least one year’s duration
- 1 in 5 individuals over the age of 65 report pain persisting for more than 24 hours in the preceding month
  - 6 in 10 report pain persisting > 1 year
- 2 out of 3 US armed forces veterans report having persistent pain attributable to military service
  - 1 in 10 take prescription medicine to manage pain

Model Policy for the Use of Controlled Substances for the Treatment of Pain*

- Pain management integral to medical practice
- Opioids may be necessary
- Physicians will not be sanctioned for prescribing opioids for legitimate medical purposes
- Under-treatment of pain will be considered a deviation from the standard of care
- Use of opioids for purposes other than analgesia threaten individuals and society
- Physicians have a responsibility to minimize abuse and diversion

*Federation of State Medical Boards, 2004
Methadone Use as an Analgesic

- Most adverse events and deaths related to methadone use are in those receiving the drug for chronic pain
- Number of methadone pain pills distributed exceeds liquid methadone used in opioid treatment
- Methadone prescriptions: 863,039 in 2000 to 4,439,850 in 2008; most frequent: 10 mg tablets
Medical Underpinnings of Adverse Events with Opioids

- U.S.: 4.6% of world’s population; consumes 80% of world opioid supplies
- U.S.: consumes 99% of world’s hydrocodone supply
Medical Underpinnings of Adverse Events with Opioids

- Syndrome of rebound pain/hyperalgesic states produced by opioid use
- Withdrawal syndromes masquerading as “pain”
- Opioid adverse events: QT prolongation, Torsade de Pointes (methadone)
- Rate of addiction and misuse had been underestimated; recent literature estimates: 4-26% have OUD; of those without OUD 10% misuse—lack of screening

Pain: How Does it Relate to Drug-Drug Interactions?

Physical (discomfort sensation) and psychological components (anxiety/depression) with overlapping treatments

- Lithium
- Stimulants
- Antipsychotics
- Beta-blockers
- Antidepressants
- Anticonvulsants
- BZDs
- NSAIDS
- Opioids
- Acetaminophen
- Steroids
Underlying Reasons for Drug-Drug Interactions

- Increasing numbers 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 you do to the drug (or not)
- Pharmacodynamic (what the drug or drugs do to you)
Pharmacokinetic Interactions

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

Rifampin effect on buprenorphine PK
McCance-Katz et al., 2011
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 buprenorphine
- Opioids and alcohol??
Opioids and Other Drugs: Basis of Adverse Events

- Why are we seeing adverse events and increasing deaths in methadone-using individuals who co-consume psychotropics: SSRIs, antipsychotics?
- Not formally studied, but…
  - DAWN and ME data describe increasing numbers
  - Methadone metabolized by CYP 3A4, 2D6, 2B6, 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 hERG 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
    - (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
    - 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 is little data to say this with certainty and drug interaction studies in this area receive little funding from NIH
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 Physicians’ Clinical Support System—Buprenorphine

- Use of Prescribers’ Clinical Support System—Opioids
Ask a clinical question…

- Get peer support for questions about practice in these areas
- 888-5pcss-b-4u (Buprenorphine)
- 855-227-2776 (Opioids)

From www.PCSSB.org and www.PCSS-O.org

- Download clinical tools, forms and concise guidances (like FAQs) on specific questions regarding opioid dependence, use of buprenorphine, safe use of opioids, training opportunities, and peer support
Please Click the Link Below to Access the Post Test for the Online Module

Upon completion of the Post Test:

• You will receive an email detailing correct answers, explanations and references for each question.
• You will be directed to a module evaluation, upon completion of which you will be emailed your module Certificate of Completion.

http://www.cvent.com/d/vcq9j9