A Review & Perspectives on Buprenorphine Diversion and Misuse: Implications for Policy and Practice

Michelle Lofwall, MD

Center on Drug and Alcohol Research
Departments of Behavioral Science &
University of Kentucky
Lexington, KY
Disclosure

- CVS Caremark: Consultant
- Braeburn Pharmaceuticals: Research study – Site Principal Investigator
Definition: Misuse of Medication

- Misuse: any use of a prescription (rx) drug that varies from accepted medical practice¹
  - By route: injection, intranasal, smoking
  - By dose: ↑ frequency (3x daily instead of once daily) or ↑ dose

- Diversion: unauthorized rerouting or appropriation of a substance

¹ASAM Board of Directors
Medication Misuse and Diversion

- The pharmacological characteristics that render opioid substitution therapies **efficacious and desirable** (i.e., opioid agonist properties) to patients are **the same characteristics** that create the risk of misuse and diversion.
How Common Are These Behaviors?

- US National Household Survey on Drug Use and Health past year use of rx psychotherapeutics (e.g., stimulants, benzodiazepines, opioid analgesics) not prescribed to them:
  - Nearly 17 million persons = ~18% of the population

- Is diversion limited to controlled substances?

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1. Substance Abuse and Mental Health Services, NHSDUH, 2013.
The Most Commonly Shared/Borrowed Medications?

- From another national survey, 23% admitted that they shared their rx drugs with others, and 27% reported that they had borrowed rx medication from another person.¹
  - 25% allergy medications
  - 22% pain relievers
  - 21% antibiotics

How Does This Compare to Patients in Medication-Assisted Treatment?

Surveys of patients enrolled in outpatient opioid addiction treatment (with either methadone or buprenorphine) report that 18-28% have sold, given away, removed it while under supervision, or shared other prescribed medication:

- Germany 23% (Stover, 2011)
- Australia 28% (Larance et al., 2011)
- United States, 18% (Caviness et al., 2013)
Questions to the Audience

How many of these statements do you agree with:

- Buprenorphine misuse and diversion
  - are a lesser evil than heroin/street drugs
  - are difficult to predict, detect or prevent
  - are unacceptable and should lead to treatment termination
  - should be assessed clinically and responded to therapeutically
Misuse/Diversion: A Lesser Evil than Heroin even if injected?

- **Consequences of injecting pharmaceuticals not intended for injection**
  - Local and systemic infections such as endocarditis\(^1,2\)
  - Overdose – risk ↑ with IV use, use with alcohol or benzos\(^3,4\)
  - US deaths: 464 through 10/2013\(^5\)

- **How to critically evaluate and respond\(^5\)**
  - Epidemiology: How common, risk factors, comparison to other medications/heroin, corrections for availability
  - Mortality & morbidity rates pre- and post-treatment expansion
  - Policy to ↓ treatment access or ↑ treatment access?

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1. Gouny et al., 1999  
2. Ho et al., 2009  
3. Reynaud et al., 1998  
4. Tracqui et al., 1998  
5. Data from Reckitt Benckiser published in Lofwall & Walsh in press Journal of Addiction Medicine
How common is injection?

- In United States, past-month injection among persons presenting for opioid abuse treatment was 45.5% for BUP vs. 16.3% for BUP/NX\(^1\).

- In Australia, all treatment with bup, bup/nx & mtd starts with supervised dosing that is available in local pharmacies\(^2\).

<table>
<thead>
<tr>
<th>Australia- weekly injection of:</th>
<th>Out-of-treatment IVDU (n=541)</th>
<th>In addiction tx with bup, bup/nx, or mtd (n=544)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUP/NX film</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>BUP/NX tablets</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>BUP tablets</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>Methadone</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

No significant difference in prevalence of weekly injection of BUP/NX film vs. tabs vs. mtd. BUP tablet injection was significantly higher than for both BUP/NX formulations.

Lessons from Finland

- By 2001, buprenorphine mono-product = most common primary opioid of abuse (surpassed heroin), including regular IV use.\(^2\) Typical treatment was detox.
- Late 1990’s: Heroin ↓ availability\(^1,2\)
- Limited access to opioid maintenance treatment\(^3,4\)
- How could this be if not much availability within Finland?
  - Part of source = from outside its borders.\(^1,2\)
  - Parallels inter-state diversion of opioid analgesics in USA (one state’s policy affecting another state’s), consequences of different state legal drinking ages
- Response: Restrict BUP availability, 2006 BUP/NX introduced

Finland: Effect of formulation & desire for opioid maintenance treatment

Out-of-treatment needle exchange participants

- 64% of the participants in 2010 reported desire to be in opioid maintenance treatment. 50% reported not being accepted into treatment (Simojoki & Alho, 2013).
Appalachia: Use of Diverted Buprenorphine

- 503 community dwelling prescription opioid abusers identified at baseline and followed over 6-months.
- At baseline, asked “Have you attempted but were unable to get into BUP treatment?”
- Evaluated for predictors of use of diverted buprenorphine “to get high” over the 6-month follow-up period using multivariable logistic regression
- Limitations: did not ask about formulation used, route of use, or other motivations for use

Lofwall and Havens, Drug and Alcohol Dependence 2012
Predictors of Use of Diverted Buprenorphine

- 471 assessed at 6-month f/u
  - 219 reported use of diverted BUP over the 6 months
  - 252 reported no use of diverted BUP

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<tr>
<th></th>
<th>Adjusted OR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tried &amp; failed access BUP tx</td>
<td>7.31</td>
<td>2.07, 25.8</td>
</tr>
<tr>
<td>Past 30 day use:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OxyContin</td>
<td>1.80</td>
<td>1.18, 2.75</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>0.53</td>
<td>0.31, 0.89</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>4.77</td>
<td>1.30, 17.5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.60</td>
<td>1.09, 2.36</td>
</tr>
<tr>
<td>DSM-IV GAD</td>
<td>1.69</td>
<td>1.11, 2.56</td>
</tr>
</tbody>
</table>
Defining Treatment Access in US

What does this mean?

- # of waived docs = ~23k in 2013 (DEA NTIS); 28% with 100 patient limit
- # dosage units or patients receiving buprenorphine:
  - 190 million dosage units in 2010 vs. 40 million in 2006 (Automation of Reports & Consolidated Orders System)
  - 800k patients in 2010 vs 150k in 2006 (DHHS 2012)
  - Do not know % prescribed for off-label pain treatment
- # taking new patients who also take Medicaid and other insurances???
- Getting quality treatment to the patients that need the treatment where and when they need it
Treatment access & diversion/misuse

- Implications for public policy
- On one hand, ↑prescribing/availability/access ↑ diversion and misuse¹ – *but*
- On the other hand:
  - Inability to access buprenorphine treatment (very few accept Medicaid) in Appalachia ↑risk of using diverted buprenorphine²
  - Remember Finland
  - And despite diversion and misuse, *can get a NET ↓in overdose deaths with treatment expansion*

¹ Cicero et al. Drug and Alcohol Depend. 2014
Baltimore: Agonist Treatment & Relationship to Heroin Overdose Deaths

1995 1997 1999 2001 2003 2005 2007 2009

0 200 400 600 800 1000 1200

Heroin Overdose Deaths

Patients in BUP Treatment

Patients in Methadone Treatment

Misuse and Diversion: Difficult to predict, detect, prevent?

- Some risk predictable from:
  - Treatment access
  - Financial incentives and training:
    - Malaysia: Expansion with no provider training, no guidelines, providers paid more $ if they dispensed (vs. prescribed) and received higher payment if prescribed more (Vicknasingham et al., 2010)
  - Pharmacological characteristics
  - Patient characteristics & their social/drug distribution networks
Misuse and Diversion: Difficult to predict, detect, prevent?

- Some can be predicted by
  - Pharmacological characteristics
  - Vast majority of epidemiological research / post-marketing surveillance shows less abuse of BUP/NX vs. BUP

- Note: Abuse deterrent features ≠ abuse-proof, no misuse
  - e.g. Methadone syrup injection
    Buprenorphine/naloxone- give small divided doses and can avoid precipitated withdrawal (Rosado et al., 2007)
Injected Buprenorphine vs. Buprenorphine/Naloxone in Morphine-dependent Subjects

Does the Drug Have Any Good Effects?

Mean Peak Rating

PL 0.25 10 8 im 8 sl
NX HM Bup

Buprenorphine /NX

 Injected Buprenorphine vs. Buprenorphine/Naloxone in Morphine-dependent Subjects


Does the Drug Have Any BAD Effects?

Mean Peak Rating

PL 0.25 10 8 im 8 sl 1/.25 2/.5 4/1 8/2 16/4

Buprenorphine/NX

Buprenorphine
Risk Management: Discussing the Harms with Patients

- Misuse and diversion lead to harmful medical consequences, including fatal overdose
- Misuse and diversion lead to harmful social consequences (e.g., arrest, jail)
- Misuse and diversion can jeopardize treatment participation and treatment availability
Patient Factors for BUP Misuse while in Treatment

- Patients in primary care (n=111) given two phone surveys (after 3 and 6 months of treatment)
- ~32% used BUP IV or IN while in OBOT\(^1,2\)

<table>
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<tr>
<th>Intravenous risk factors</th>
<th>Odds ratio</th>
</tr>
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<tbody>
<tr>
<td>Perceived dose inadequate (Median 6 mg daily)</td>
<td>2.9</td>
</tr>
<tr>
<td>Hx suicidal ideation/attempt</td>
<td>2.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intranasal risk factors</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx IN drug use</td>
<td>5.6</td>
</tr>
<tr>
<td>Growing up with 0/1 parent</td>
<td>4.0</td>
</tr>
<tr>
<td>Unstable living</td>
<td>2.5</td>
</tr>
<tr>
<td>Unsatisfied with tx</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Risks for Misuse and Diversion

- Pseudopatients or “double-dippers” seeking to divert drug
Risk Management: Comprehensive Evaluation at Intake

Before initiating treatment

- Checking available state prescription monitoring programs to ensure patient is receiving treatment from only you
- Confirm diagnosis
  - Positive urine test for opioids
  - Consistent subjective patient history
  - Corroborating evidence on examination
  - Signs/symptoms of opioid withdrawal (COWS)
Risks for Misuse and Diversion

- Pseudopatients or “double-dippers” seeking to divert drug
- Under-prescribing
  - Inadequate withdrawal suppression
  - Inadequate opioid blockade
Methadone: Heroin Self-administration


Methadone (p.o. day)
- 50 mg
- 100 mg
- 150 mg

Heroin (mg / 70kg, Iv)

# of injection choices

0 1 2 3 4 5 6 7

0 10 20
Buprenorphine: Heroin Self-administration

Risks for Misuse and Diversion

- Pseudopatients seeking to divert drug
- Under-prescribing
- Over-prescribing
Average Daily Maintenance Dose

Risks for Misuse and Diversion

- Pseudopatients seeking to divert drug
- Under-prescribing
- Over-prescribing
- Failure to address the disorder beyond medication
What can physician’s do to decrease the risk of misuse/diversion?

- Careful screening at intake
- Regular review and monitoring of dose adequacy and treatment response
- Increase supervision for those patients who are unstable or who have shown past evidence of misuse or diversion
- Urine drug screens (ensure presence of treatment agent [and relevant metabolites])
- Contingency management
- Medication counts
- Treatment contracts
- Address the full psychosocial spectrum of the disorder
Mentors

Pharmacy collaboration

Objective monitoring of outcomes

Psychosocial & behavioral treatments

Appropriate & therapeutic prescribing practices

Therapeutic doctor-patient relationship
Conclusions

- Diversion & misuse are common behaviors that are not limited to controlled substances
- Medications with agonist properties will be associated with the risk of abuse, misuse and diversion
- Data show that buprenorphine/naloxone has less risk compared to others, but the absolute risk is dependent on many factors other than pharmacology
Conclusions

- Physicians can reduce these risks through thorough assessment, patient education, appropriate dosing and prescribing, and engaging in quality care practices.
- Need careful public policy understanding that cutting off treatment access or greatly it will not eliminate or guarantee diversion and misuse and may adversely affect mortality rates.
Questions & Cases for Next Webinar

- Wednesday September 24, 2014 12:00 pm - 1:00 pm (ET) *Clinical Case Reviews: Managing Diversion and Misuse in Office-Based Treatment*

- Please submit cases that can be discussed (remove any identifying information) for this webinar to: pcssmat@psych.org.