Resisting Temptation: Can Abuse-Deterrent Formulations Curb Opioid Abuse?

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Disclosures

• Dr. Keast declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

• Dr. Fudin declares the following:
  - Kaléo (Speakers Bureau, Advisory Board)
  - KemPharm (Consultant)
  - Millennium Health, LLC (Speakers Bureau)
  - Remitigate, LLC (Founder, Owner)
  - Scilex Pharmaceuticals (Consultant)
  - Zogenix (Consultant)
  - Faculty (PainWeek; PainWeekEnds)

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Learning Objectives

1. Explain how altering opioid formulations for abuse affects their kinetics and increases overdose risks
2. Compare and contrast tamper-deterrent opioid formulations and other pharmacological approaches to deter abuse
3. Describe validated risk assessment tool applicability for employing universal precautions and how this could apply to tamper-deterrent preference
4. Describe national and state efforts to curb abuse and misuse
5. Describe issues surrounding the selection of tamper-resistant products for individual patients

Which of the following factors does not influence the likability of opioids for abuse?

A. Media attention
B. High first-pass metabolism
C. Tampering susceptibility
D. Peer preferences

Embeda and Suboxone are examples of which type of approach to abuse-deterrent formulations (ADFs)?

A. Physical barrier
B. Viscosity management
C. Sequestered antagonist
D. Aversion agent
What 2 pharmacokinetic properties are exploited to increase abuse potential?
A. Half-life and elimination factor
B. Maximum plasma concentration and time to peak concentration
C. Receptor binding affinity and excretion factor
D. Enzyme degradation and pro-drug metabolism

Which of the following national organizations have developed plans to curb misuse of prescription opioids?
A. Center for Disease Control and Prevention
B. Center for Medicare and Medicaid Services
C. Office of the President
D. All of the above

Which of the following characteristics is NOT associated with high nonmedical opioid use or use disorders?
A. Sedative use disorder
B. Disabled for work
C. Private insurance
D. Depression

Introduction
Current State of Prescription Drug Abuse Epidemic
Dr. Shellie Keast

The Prescription Drug Abuse Epidemic

Nonmedical Use of Pain Relievers (NMPR)
- 4.3 million used prescription pain relievers for nonmedical purposes (1.6% of population)¹
- Use has decreased from 2002, but plateaued beginning in 2013¹
- Marijuana, prescription pain relievers, and cocaine remain the main issues of concern¹-²

Heroin Use

- 460 people aged 12 or over start using heroin every day
- Mortality has increased since 2000
- Use remains below 0.3% of the 12 or over population
- Strong association between NMPR and past year initiation of heroin
- Recent use of heroin was 19 times higher for those with NMPR use
- Although gateway theory is supported, most NMPR users do not progress to heroin use.

References (for Introduction slides)

Risk Assessment
Validated Risk Tools and Monitoring
Dr. Jeffrey Fudin
Risk Assessment Tool

- Why is it important to assess risks?
  - Safety
  - Public health (diversion, death, naloxone access)
- What are the risks?
  - Drug interactions (anticipated and unanticipated)
  - Aberrant behaviors and UNIVERSAL PRECAUTIONS
- Collaboration with Clinics/providers
  - Role of the pharmacist (clinic and community)
    - Assess risk, patient monitoring, UDT, community outreach, in-home naloxone qualification
- Opioid Risk Stratification Tools Summarized (next slide)

Opioid Misuse Tools

<table>
<thead>
<tr>
<th>Question</th>
<th>Formats</th>
<th>Indications</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Scoring</th>
<th>Validated</th>
</tr>
</thead>
<tbody>
<tr>
<td>PADT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
<td>12 clinical parameters based on 3-4-A's</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- Documents program over reaffirmation of clinical evaluation
- Not intended to be a predictor of drug-seeking behavior or to determine necessity of opioid therapy | 
- Not intended to predict the need for or necessity of opioid therapy | 1 yes, 4 no | Y/N answers |
| COMM<sup>4</sup> | No | 
- 8 item questionnaire
- Categorizes patients as low, moderate, high risk | 
- Long and complicated to use
- Variables of scoreable elements | 
- Cannot be used as a screening tool for those with scores less than 2 | 1 question in the VHA setting | 

Street Value Perspective

- 120 Percocet 5/325 (brand name)
  - $600.00
- 120 Lortab 10/500 (any brand)
  - $600.00
- 60 Oxycontin 80mg
  - $1500.00
- 120 Actiq Lollipop 200mcg
  - $3240.00

Knowing when your patient is diverting drug... PRICELESS!

http://streetrx.com/

Do you sell these?

[Image of products for sale]

The Clean Whiz Kit

(http://www.youtube.com/watch?v=91knqsnu_hU)
Urine Drug Testing (UDT) Rationale

• Guidelines recommend UDT as standard of care when prescribing chronic opioid therapy, especially for CNCP.
• Helps to ensure compliance and mitigate risk.
• Detects presence of illicit substances.
• Detects absence of prescribed medication.
• Helps to justify continual prescriptions.
• Supports clinician decision to discontinue controlled substance medication.

Urine Drug Testing (UDT) Rationale

• Supports justification for closer monitoring (more frequent visits / lab monitoring).
• Supports behavior modification and referral to psychologist.

Potential Pitfalls:

• Patient reliability to report compliance, use and misuse is dubious and often poor.
• Behavior alone is unreliable for identifying patients at risk non-compliance, abuse, misuse, and diversion.

References (for UDT slides)


Types of Urine Drug Testing

Immune Assay (IA)

• In office or send out.
• Inexpensive.
• Results are quick (minutes).
• Helps for initial detection.
• False negatives/positives.
• False patient accusations.
• Easier for pts to manipulate.
• Low sensitivity, esp w/ synthetics.
• Presence/absence of RX class only.
• No option for synthetics, designer drugs, and unique natural products.

Chromatography

• Usually send-out.
• More expensive.
• 24 hours to 1 week (per lab).
• Final result.
• Definitive testing.
• Justifies RX decisions.
• 99.999 percent reliability high sensitivity.
• Presence/absence of RX metabolites.
• Custom option for synthetics, designer drugs, and unique natural products.

Opioid Chemistry and Cross-sensitivity

Phenyl-Propylamines

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### What medications are prescribed to the patient?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mgs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>meloxicam</td>
<td>20</td>
</tr>
<tr>
<td>meperidine</td>
<td>250</td>
</tr>
<tr>
<td>naproxen</td>
<td>1000</td>
</tr>
</tbody>
</table>

### Select result from urine drug test

- **Opiates (Cut-off ≤100ng/mL)**: Negative
- **Benzodiazepines**: Negative
- **Amphetamines**: Positive
- **Barbiturates**: Negative
- **Cannabis**: Positive
- **Cocaine**: Negative
- **PCP (Phencyclidine)**: Positive

### Recommendations:

**Cocaine Test:** Negative, result expected.

**PCP Test:** Positive, result not unexpected because false positive, verapamil detected. Click here for a full list of false positives. Urinetmp recommends discussing findings with patient, using clinical judgment, and if indicated, definitive testing by quantitative confirmation.

**Benzodiazepines Test:** Negative, result not unexpected because the prescribed benzodiazepine(s) can provide a full list of false positives. Urinetmp recommends discussing findings with patient, using clinical judgment, and if indicated, definitive testing by quantitative confirmation.

**Positive amphetamine is possible because an prescribing carbamazepine which listed false at false positive. The patient may be taking an uncontrolled opiate and a benzodiazepine, as indicated by Urinetmp below. The other unexpected results are possible because of prescribed medications.

### Fill out the fields below as needed:

- **Patient name:** Mr. Bad Urine Test
- **Data entry by:** Ms. Dedicated LPN
- **Ordering clinician:** Dr. Smith
- **Clinician notes:** Positive amphetamine is possible because an prescribing carbamazepine which listed false at false positive. The patient may be taking an uncontrolled opiate and a benzodiazepine, as indicated by Urinetmp below. The other unexpected results are possible because of prescribed medications.

### Printout

**COCAINETEST:** Negative, result expected.

**PCP TEST:** Positive, result not unexpected because false positive, verapamil detected. For a full list of false positives, see list in Urinetmp recommends discussing findings with patient, using clinical judgment, and if indicated, definitive testing by quantitative confirmation.

**BENZODIAZEPINES TEST:** Negative, result expected because the prescribed benzodiazepine(s) can provide a negative result. Urinetmp recommends discussing findings with patient, using clinical judgment, and if indicated, definitive testing by quantitative confirmation.

**AMPHETAMINES TEST:** Positive, result expected because false positive, verapamil detected. For a full list of false positives, see list in Urinetmp recommends discussing findings with patient, using clinical judgment, and if indicated, definitive testing by quantitative confirmation.

**CANNABIS TEST:** Positive, result expected because false positive, verapamil detected. For a full list of false positives, see list in Urinetmp recommends discussing findings with patient, using clinical judgment, and if indicated, definitive testing by quantitative confirmation.

**AMPETAMINES TEST:** Negative, result expected because false positive, verapamil detected. For a full list of false positives, see list in Urinetmp recommends discussing findings with patient, using clinical judgment, and if indicated, definitive testing by quantitative confirmation.

### Printout continued

**WARNING:** RISK OF OPIS TOXICITY INCLUDING RESPIRATORY DEPRESSION, OVERDOSE, AND DEATH ARE ELEVATED WHEN CONSUMING OPIODS WITH BISCUIT/ALZEDINES OR ETHANOL. IF CLINICALLY WARRANTED, CONSIDER TAPERING OPIODS OR THE NEGATIVE ANXIETY.
Efforts to Curb Misuse
Recent National and State Efforts
Dr. Shellie Keast

Recent National Efforts to Curb Misuse
• 2010 – First abuse-deterrent opioid introduced (oxycodone extended-release)
• 2011 – Obama Administration detailed a response to the drug abuse crisis¹
• 2012 – CMS issues strategies to reduce diversion in Medicaid²
• 2013 – FDA required changes to long-acting and extended release opioid pain medications and released draft guidance on abuse-deterrent opioids³

Recent National Efforts to Curb Misuse, Cont.
• 2015 – Issues final guidance to industry regarding abuse-deterrent opioids⁴
• 2015 – Obama Administration announced new steps to increase access to drug treatment⁵
• 2015 – CDC launches Prescription Drug Overdose: Prevention for states⁶

State Efforts
• States have also initiated efforts to curb abuse
• Kentucky enacted a strict mandate for PDMP (2012)
• Massachusetts developed a comprehensive strategy to end opioid abuse (2014)
• Arizona issued opioid prescribing guidelines (2014)
• Wisconsin begins “Dose of Reality” media campaign (2015)
• The list goes on…..

Oklahoma’s History
• Medicaid policies to curb abuse and misuse⁷:
  – 2003 to 2015: 13 unique policies implemented
  – Various levels of success
• Governor’s task on prescription opioid abuse (2012)
• Senate study on opioids with abuse-deterrent properties (2015)
• General agreement that solution requires collaborative effort between state agencies and communities

Research on Effect of Abuse-Deterrent Opioids
• Largely centered around oxycodone extended-release⁸⁻¹⁷
• Changes in use of oxycodone extended-release after release of new formulation¹⁸
  – Decrease from 46% to 26% in past-month use in first year
  – 33% of abuser of original formulation continued to abuse new
  – 33% of abusers of original changed drugs
  – 5% indicated new influenced decision to stop abusing drugs
• Most who continued abusing either changed to oral route or defeated the abuse-deterrent mechanism
• 70% who switched drugs turned to heroin

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Research on Effect of Abuse-Deterrent Opioids

- Introduction of new formulation of oxycodone extended-release resulted in reduced sales, but did not result in a statistically significant change in overall opioid market.
- Hwang and colleagues\(^{13}\):
  - Large portion of opioid abusers use oral route which abuse-deterrent opioids do not effect
  - New agents may cause practitioners to have a false sense of security in prescribing new formulations

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References (for Efforts to Curb Misuse slides)

5. FACT SHEET: Obama Administration Announces Public and Private Sector Efforts to Address Prescription Drug Abuse and Heroin Use

12-Month Summary of Costs per Enrollee in US dollars: Median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>Generic (N=541)</th>
<th>New Formulations (N=397)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx Costs</td>
<td>$3,854 (5,097)</td>
<td>$12,167 (19,745)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Opioid Rx Costs</td>
<td>$1,532 (1,747)</td>
<td>$9,922 (7,138)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Medical Costs</td>
<td>$9,306 (17,187)</td>
<td>$10,015 (19,622)</td>
<td>0.38</td>
</tr>
<tr>
<td>Healthcare Costs</td>
<td>$15,043 (22,996)</td>
<td>$24,979 (34,971)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

References (for Efforts to Curb Misuse slides)

**Physical Barriers**

- Shelter "or "entrap" the active drug
- Control or avert enhancement of delivery
  - Characteristics of barriers
    - Resist physical manipulation
    - crushing / grinding
    - As a result, mitigate against
      - Snorting
      - Smoking
      - Extraction
    » for "dose dumping"
    » for rapid absorption via intravenous administration

**Viscosity Management**

- **Exciptent**
- **Swelling and Increased Viscosity**
  - water-soluble/swellable cellulose derivatives
  - polyethylene oxide, gums, clays and polyacid carboxomers
  - consequential increase in solution viscosity
  - drug trapping in a gel-like substance
  » prevents syringe extraction for intravenous use

**Viscosity Management (continued)**

- **Sorption Processing**
  - physical and chemical process by which one substance becomes attached to another. Options include:
  1. Ion-exchange resins to bind and trap free drug if tamper attempted
  2. drug already attached to crush-resistant resin particles
  - prevents rapid release of the drug in common, extraction solvents
  3. Modification of solubility (temperature, pH, particle size and solvent)
  - To affect drug's absorption
    » Example: meglumine, a basic solubilizing agent
    » in the presence of methadone, can increase the pH causing methadone to precipitate out rendering it more difficult for extraction for oral liquid or injection

**In vivo Processes**

- Modifying or interfere with drug binding or metabolism following the administration of a product into the body
  - Opioid antagonists
  - Prodrugs
  - Enzyme inhibitors

**Examples**

- Talwin NX (pentazocine + naloxone)
- Suboxone (buprenorphine + sequestered naloxone)
- Embeda (morphine + sequestered naltrexone)
- Zubsolv (buprenorphine + naloxone)
- Targin ER (oxycodeone + naloxone)
Other In vivo Options
Inactive prodrug mitigates against...
- Parenteral
- Nasal
- Smoking
• Pharmacokinetic advantages...
  - Extends time to peak
  - Possibly lessen the euphoric effects
Enzyme inhibitors
  - Inhibit or slow the transformation to drug to active metabolite
Sequestered metabolic blocking agents
  - Released upon administration of a tampered product
  - Deter abuse by crushing or chewing for snorting or parenteral administration
  - Advantage over antagonist formulations, blunted immediate withdrawal

Modifying Drug Favorability
• Oxecta has 2 unique abuse deterrent properties
  - Sodium lauryl sulfate - snorting becomes unpleasant
  - Excipient results in gel formation with attempt to dissolve
• Previous to Oxecta
  - Acurox
    • Oxycodone + niacin
• Other Aversive Options
  - Constituents that trigger unpleasant and very noxious SEs
    - Laxatives (ex. bisacodyl, casanthanol, senna), nauseants (zinc salts, ipecac, cephaeline), bittering agents (ex. menthol, eucalyptus oil, denatonium benzoate, denatonium saccharide), and mucous membrane irritants (resiniferatoxin, olvanil, sodium lauryl sulfate)

Patient Selection
Dr. Shellie Keast

Right Drug for the Right Patient
• Choosing the proper patient for an abuse-deterrent product may not be straightforward
• Choice may be based more on who is most likely to abuse opioids
• Characteristics associated with high nonmedical use or use disorders (Han 2015):
  - Sedative use disorders
  - Other substance disorders (nicotine, etc)
  - Disabled for work
  - Medicaid as primary insurance
  - Depression, mental health diagnoses

Right Drug for the Right Patient
• Incorporate risk assessment tools before prescribing
• Perform frequent Urine Drug Testing
• Utilization of PDMP monitoring systems by all providers
• Have a plan to discontinue opioids prior to initiation
• Pain management patient contracts
  - Provide structure, support, and monitoring
• Know the demographics and abuse rates in your practice area
• Remember that abuse-deterrent opioids can still be abused by oral route of administration

Manipulating the ADF
And Altered Pharmacokinetics
Dr. Jeffrey Fudin
One step forward, two steps back

Where to buy them...
https://www.youtube.com/watch?v=XemdKyIrwUo

Overcoming Abuse Deterrent Tablets
https://www.youtube.com/watch?v=2pnfuz2_y0Y

Pharmacist & Community Service
Can we help?
https://www.youtube.com/results?search_query=evzio+fudin

Trying to help other addicts...
Buy Oxycodeone, Hydrocodeone, Methadone Online
https://www.youtube.com/watch?v=KE8NFd4TUVe
Key Points

- Nonmedical use of pain relievers continues to be an important medical and societal problem.
- Abuse-deterrent formulations are being developed to "meaningfully deter abuse" through non-oral routes.
- Patients with increase substance abuse risk include male gender, family and/or personal hx substance abuse, smoker, alcoholism, PTSD, schizophrenia
- National and state entities are actively involved in efforts to curb misuse
- Current research into abuse-deterrent formulations indicate some decrease in non-oral misuse, but heroin use may be increasing
- ADF's do not prevent abuse; they mitigate risks

Key Points

- Selecting the right patient for these formulations is challenging – planning and monitoring are the key
- ADF's are not created equal
  - Some deter abuse by injecting oral formulations
  - Some deter abuse by snorting
  - Some deter dose-dumping when ingested with alcohol
  - All can be taken in large quantities and cause death
    • Newer formulation on the way may overcome this

Which of the following factors does not influence the likability of opioids for abuse?

A. Media attention
B. High first-pass metabolism
C. Tampering susceptibility
D. Peer preferences

ANSWER: B. Factors that influence opioid abuse attractiveness include media attention, peer preferences, low cost, availability, tampering susceptibility, and a high attractiveness quotient (high Cmax, low Tmax).

Embeda and Suboxone are examples of which type of approach to abuse-deterrent formulations (ADFs)?

A. Physical barrier
B. Viscosity management
C. Sequestered antagonist
D. Aversion agent

ANSWER: C. Embeda and Suboxone contain sequestered naltrexone and naloxone, respectively.

What 2 pharmacokinetic properties are exploited to increase abuse potential?

A. Half-life and elimination factor
B. Maximum plasma concentration and time to peak concentration
C. Receptor binding affinity and excretion factor
D. Enzyme degradation and pro-drug metabolism

ANSWER: B. An increased maximum plasma concentration (Cmax) and decreased time to maximum concentration (Tmax) increase abuse potential.

Which of the following national organizations have developed plans to curb misuse of prescription opioids?

A. Center for Disease Control and Prevention
B. Center for Medicare and Medicaid Services
C. Office of the President
D. All of the above

ANSWER: D. All of the listed organizations have developed plans to curb misuse. States have also developed localized plans to curb misuse.
Which of the following characteristics is NOT associated with high nonmedical opioid use or use disorders?

A. Sedative use disorder  
B. Disabled for work  
C. Private insurance  
D. Depression

ANSWER: C. Medicaid as primary insurance is a characteristic associated with high nonmedical opioid use or use disorder.