National Academy of Medicine
Session 4

Opioid Analgesics with Abuse-Deterrent Properties: Current Data and Future Opportunities

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Opioids with Abuse Deterrent Properties: Current Data and Future Opportunities

- Oxycodone ER fulfills the Hill criteria for causation
  - Plausibility
  - Temporality
  - Effect Size
  - Consistency
  - Specificity
  - Alternative explanations

- Questions and Issues
  - National Academy of Science
  - US Food and Drug Administration
Hill Criteria: *Plausibility*

- A plausible mechanism between cause and effect is helpful (but understanding of the mechanism is limited by current knowledge)

Prescription drug abuse is like other drug abuse, except with an additional “route” of abuse:
- Oral = intact + *chewed or crushed*
- Intranasal
- Intravenous

Importance of manipulating drug
- Crucial transition
  - Changes perception of heroin use\(^1\)
  - Risk of acute (overdose, death) and chronic events (addiction, infections, death) higher after intranasal or IV abuse than oral abuse

Biological Plausibility

Filling the Balloon

Person in Pain

Susceptible Person

Recreational Abuser

Outcomes

Addiction

Overdose

Death

Intact → Chewed → Crushed

Recapitulation

Person in Pain → Susceptible Person → Recreational Abuser

Intervening in Prescription Drug Abuse

Emptying the Balloon

Person in Pain

Guidelines

Susceptible Person

Recreational Abuser

Intact

Chewed

Crushed

Outcomes

Addiction

Overdose

Death

Hill Criteria: *Temporality*

- Effect has to occur after the cause (including a delay, if expected)
- Minimal delay expected for oxycodone ER
  - All drug shipped after August 9, 2010 was reformulated version
  - Pharmacy turnover of opioids is rapid
- Only oxycodone ER has adequate data to evaluate effectiveness

Oxycodone ER Prescriptions Dispensed Decreased Promptly After Reformulation

Other Opioids = Oral dosage forms of opioid analgesics: hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and IR oxycodone

IMS, 2015
RADARS® System Surveillance of Prescription Drug Abuse

- Independent postmarketing surveillance program focusing solely on prescription drug abuse
- Most manufacturers of prescription opioids are subscribers
  - Limited to use for regulatory and risk-management use

Acute Health Events
Entering Treatment
New Initiates
Web Monitoring
Drug Transactions
Entering Treatment
Illicit Market Price
Why Adjust for Population?

Population-adjusted Rate = \frac{\# \text{ Events in Geographic Area}}{\text{Population in same Geographic Area}}

- Accounts for obtaining drug (reduction in doctor shopping)
- Abuse after prescription is dispensed
- \textbf{What if we had a perfect ADF?}
  - ↓ doctor shopping, ↓ pill mill activity
  - ↓ high risk abuse after Rx
Temporality: 3 Phases of Oxycodone ER Abuse and Diversion, Adjusted for Population, 2010 – 2016Q2
Hill Criteria: *Effect Size*

- A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.

Effect Size: Oxycodone ER Abuse and Diversion, Adjusted for Population, 2010-2016

Poison Center – Intentional Abuse

Drug Diversion Investigations

Opioid Treatment – Abuse

Survey Key Informant Patients – Abuse
Hill Criteria: Consistency

- Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect
Consistency: Oxycodone ER Associated with Lower Rates Across Many Data Sources

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Source</th>
<th>Pre vs. Post % Change [95% CI] Since Reformulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misuse</td>
<td>RADARS (Poison Centers)</td>
<td></td>
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<td></td>
<td>RADARS (Poison Centers)</td>
<td></td>
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<tr>
<td></td>
<td>NPDS (Poison Centers)</td>
<td></td>
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<tr>
<td>Abuse</td>
<td>NAVIPPRO (Treatment Centers)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RADARS SKIP (Treatment Centers)</td>
<td></td>
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<td></td>
<td>RADARS OTP (Treatment Centers)</td>
<td></td>
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<tr>
<td>Opioid Use Disorder</td>
<td>Database of Opioid Users (Marketscan)</td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>Database of Opioid Users (Marketscan)</td>
<td></td>
</tr>
<tr>
<td>Diversion</td>
<td>RADARS (Drug Diversion)</td>
<td></td>
</tr>
<tr>
<td>Doctor Shopping</td>
<td>IMS Prescription Data</td>
<td></td>
</tr>
</tbody>
</table>

Data adjusted for prescription volume

National Survey of Drug Use and Health, OxyContin Nonmedical Use

Introduction of Reformulated Oxycodone ER

# Cases of Past Year Nonmedical OxyContin Use (in millions)
Poison Center Cases: Response to Reformulation of Oxycodone ER and Oxymorphone ER

**Oxycodone ER**

Reformulation of: OxyC ER OxyM ER

**Oxymorphone ER**

Reformulation of: OxyC ER OxyM ER

**Other Opioids**

Reformulation of: OxyC ER OxyM ER

Rate per 100,000 population
Hill Criteria: Specificity

- The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship\(^1\)
- Results specific to oxycodone ER compared to other analgesic opioids
- FDA Concerns\(^2\)

2. International Society of Pharmacoepidemiology, August 26, 2015
“For data streams that collect information on a variety of events (e.g., abuse, adverse reactions), changes should be limited to abuse-related categories”
“For evaluation of ADFs, changes should be seen only in the routes of abuse expected to be affected”

All routes of abuse should be low with an effective ADF
Alternate Explanations Fail the Temporality and Specificity Criteria

Oxycodone ER
All Other Opioids

PDMP Initiation

Per 100,000 Population


Reformulation
WA Rx Guidelines
Natl Drug Take Back

FL TIRF REMS
ER/LA REMS
HC-APAP Tramadol

NY/ACEP Rx Guidelines

PDMP Initiation

Per 100,000 Population

0 0.02 0.04 0.06 0.08 0.1 0.12

Oxycodone ER
All Other Opioids
Other Issues

- Effect of ADFs on opioid related harm in the community
- FDA policies and procedures of review, approval, and monitoring
- Gaps in Research
- Immediate Release vs. Extended Release Formulations
Effect of Abuse Deterrent Opioids on Opioid-Related Harm in the Community

- Extended release products have a small part of opioid market
- ER products account for small portion of total abuse
- Oxycodone ER can reduce its own abuse, not entire market
FDA Policies and Procedures

Gaps in Research

- Guidance was excellent beginning
- Definitions
  - Meaningful reduction
  - Addiction, Overdose
  - Totality of the evidence – no framework to address
- Comparator drugs
- IR/ER – abuse usually starts on IR, but no special risk management
Conclusions and Implications

- Specificity, consistency and effect size indicate that abuse deterrent opioids are likely to be effective in reducing abuse and its outcomes.
- Similar effects for crush-resistant oxymorphone ER.
- Widespread use would reduce prices and reduce the crucial transition from intact swallowing to crushing.
- Education, training, and other interventions needed as well.
Backup Slides
Temporality: Oxycodone ER Abuse and Diversion, Dosage Units Dispensed, 2010-2016

Poison Center – Intentional Abuse

Drug Diversion Investigations

Opioid Treatment – Abuse

Survey Key Informant Patients – Abuse
Effect Size: Oxycodone ER Abuse and Diversion, Adjusted Dosing Units Dispensed, 2009-2016
Specificity of Reduction in Abuse of Oxycodone ER

Abuse
Misuse
Suicide
Unintentional therapeutic error
Unintentional general exposure

Relative change in dosing units dispensed rate
Specificity of Reduction in Abuse of Oxycodone ER by Route

Relative change in dosing units dispensed rate

Inhale or Inject

Oral
ADFs Will Increase Opioid Use: ER Opioid Prescriptions Have Been Decreasing Over Last 5 Years
IV and Intranasal Opioid Abuse Associated With Higher Risk of Death or Major Effects

<table>
<thead>
<tr>
<th>Route of Abuse</th>
<th>Relative Risk of Death or Major Effect</th>
<th>Relative Risk [95% CI]</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compared to Oral Ingestion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intranasal</td>
<td></td>
<td>2.2 [1.7, 3.0]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td>2.6 [2.0, 3.4]</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

RADARS System Poison Center Program, 2015 Data on File
Reformulated Oxycodone ER Replaced Original Formulation Quickly
Did Introduction of Oxycodone ER Cause an Increase in Heroin Abuse?

E National Survey on Drug Use and Health

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Persons Reporting Heroin Use in Past Month</th>
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<tbody>
<tr>
<td>2002</td>
<td>180,000</td>
</tr>
<tr>
<td>2003</td>
<td>190,000</td>
</tr>
<tr>
<td>2004</td>
<td>180,000</td>
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<td>2005</td>
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<td>2010</td>
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<td>2011</td>
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<td>2012</td>
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<td>2013</td>
<td>180,000</td>
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Release of reformulated OxyContin

Approaches to Abuse Deterrence

- Physical / chemical barriers
  - Hydrocodone (Hysingla®, Vantrela®)
  - Morphine (Arymo®, Morphabond®)
  - Oxycodone (OxyContin®, Xtampza®)

- Agonist / antagonist
  - Morphine (Embeda®)
  - Oxycodone (Troxyca® ER)

- Aversion

- Delivery System (incl. depot forms and implants)

- New molecular entities and prodrugs

- Combination – Two or more methods combined

- Novel approaches
Abuse-Deterrent ER Oxycodone Reduces IV Abuse in Australia

Street Price of Reformulated Oxycodone ER 45% Lower Than Original Version

Oxycodone ER Price, 2011

Median Dollar per milligram

- $1.00 for OxyContin, crushable
- $0.55 for OxyContin, reformulated

StreetRx.com, 2016
# Events in Geographic Area

- Evaluates abuse after user has obtained the drug
- Does not include reduction in doctor shopping or prescribing behavior

# Dosage Units Dispensed

- Accounts for obtaining drug (reduction in doctor shopping)
- Abuse after prescription is dispensed
- What if we had a perfect ADF?
  - ↓ doctor shopping, ↓ pill mill activity
  - ↓ high risk abuse after Rx

Population

\[
\frac{\text{# Events in Geographic Area}}{\text{Population in same Geographic Area}} = \frac{\text{Population}}{\text{Population}}
\]

Dosage Units Dispensed

\[
\frac{\text{# Events in Geographic Area}}{\text{# Dosage Units Dispensed in same Geographic Area}} = \frac{\text{Population}}{\text{Population}}
\]