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

International Society of Pharmacoepidemiology, August 26, 2015
A plausible mechanism between cause and effect is helpful (but understanding of the mechanism is limited by current knowledge)
Scientific Basis of Abuse-Deterrent Opioids

- 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

Person in Pain

Susceptible Person

Recreational Abuser

Filling the Balloon

Intact → Chewed → Crushed

Outcomes
- Addiction
- Overdose
- Death
Intervening in Prescription Drug Abuse

Emptying the Balloon

Outcomes
- Addiction
- Overdose
- Death

Person in Pain
Guidelines
Susceptible Person
Recreational Abuser

Intact → Chewed → Crushed

PDMP
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
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
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
- **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
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>
</tr>
<tr>
<td>Abuse</td>
<td>RADARS (Poison Centers)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPDS (Poison Centers)</td>
<td></td>
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<tr>
<td></td>
<td>NAVIPPRO (Treatment Centers)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RADARS SKIP (Treatment Centers)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RADARS OTP (Treatment Centers)</td>
<td></td>
</tr>
<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

- Graphs showing the rate per 100,000 population over the years 2010 to 2014.

- The graphs display changes in rates corresponding to the reformulation events.
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
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
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
Effect Size: Oxycodone ER Abuse and Diversion, Adjusted Dosing Units Dispensed, 2009-2016

### Poison Center – Intentional Abuse

- % Change Since Q3 2010
- % Change Since Q3 2010

### Drug Diversion Investigations

- % Change Since Q3 2010
- % Change Since Q3 2010

### Opioid Treatment – Abuse

- % Change Since Q3 2010
- % Change Since Q3 2010

### Survey Key Informant Patients – Abuse

- % Change Since Q3 2010
- % Change Since Q3 2010

Reformulation of Oxycodone ER
Specificity of Reduction in Abuse of Oxycodone ER
Specificity of Reduction in Abuse of Oxycodone ER by Route

Inhale or Inject

Oral

Relative change in dosing units dispensed rate

-100%  -50%   0%   50%   100%
ADFs Will Increase Opioid Use: ER Opioid Prescriptions Have Been Decreasing Over Last 5 Years

IMS National Prescription Audit (2011-2015)
**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>
</tr>
</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

No. of Persons Reporting Heroin Use in Past Month

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

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

StreetRx.com, 2016
Adjustment for Population or Dosing Units Provides Different Perspectives

### Population

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

- 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
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### Dosage Units Dispensed

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

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