Abuse Deterrent Formulations: Testing effectiveness from the benchtop to real world

Do Medications with Abuse Deterrent Properties Work in the Real World?

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Judging by the size and frequency of the droppings, I’d say we’ve found the campaign trail.
ADFs in the Real World

• Category 4
  – Epidemiological evaluation
  – Evaluates the performance of the product in the real world
  – No product has yet requested Category 4 designation

• Methods of deterring abuse
  – OxyContin (oxycodone) and Arymo (morphine) use a physical-chemical approach that produces a tablet that is hard to crush and forms a thick gel with water.
  – Embeda (morphine) uses naltrexone as an antagonist to reduce the desired drug effect if the product is crushed.
  – Xtampza (oxycodone) uses a proprietary waxy microsphere that is difficult to crush or solubilize.
Hill Criteria: Do ADFs Work in the Real World?

• **Strength** (effect size)
• **Consistency** (reproducibility)
• **Specificity**
• **Temporality** (Effect has to occur after the cause)
• **Biological gradient**
• **Plausibility**
• **Coherence**
• **Experiment**
• **Analogy**
• **Confounding factors**
Hill Criteria: *Plausibility*

- 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
  – 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

Intact → Chewed → Crushed

Outcomes

Addiction

Overdose

Death

Intervening in Prescription Drug Abuse

Emptying the Balloon

Person in Pain

Guidelines

Susceptible Person

Recreational Abuser

Intact

Chewed

Crushed

Outcomes
- Addiction
- Overdose
- Death

Person

Addiction

Overdose

Death

Intervening in Prescription Drug Abuse

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

Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS System)

History
  - 2002, launched by Purdue Pharma
  - 2006, Denver Health and Hospital Authority takes independent ownership
    - Denver Public Hospital for 150 years
    - State sanctioned independent authority

Conflict of Interest Statement
- Most manufacturers of prescription opioids or stimulants subscribe to RADARS System.
- Subscribers receive information, but do not participate in developing the System, data collection, or analysis of the data. They do not have access to the raw data.
- Employees are prohibited from personal financial relationships with any other company.
Mosaic Surveillance

Diagram showing various components:
- Poison Center
- Acute Health Events
- Opioid Treatment
- Patients in Treatment
- Survey of Non-Medical Use of Prescription Drugs
- General Adult Population
- Web Monitoring
- Early Signals/Contextual Experience
- College Survey
- Early Experimenters
- StreetRx
- Users/Buyers
- Drug Diversion
- Criminal Justice/Law Enforcement
- Survey of Key Informants' Patients
- Patients in Treatment
Temporality: Oxycodone ER Prescriptions Decreased Promptly After Reformulation

Other Opioids = Oral dosage forms of opioid analgesics: hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and IR oxycodone
Temporality: Oxycodone ER Abuse and Diversion, Adjusted for Population, 2010–2016
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>
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</thead>
<tbody>
<tr>
<td>Misuse</td>
<td>RADARS (Poison Centers)</td>
<td></td>
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<tr>
<td>Abuse</td>
<td>RADARS (Poison Centers)</td>
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<td>NAVIPPRO (Treatment Centers)</td>
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<td>RADARS SKIP (Treatment Centers)</td>
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<td>RADARS OTP (Treatment Centers)</td>
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<td>Opioid Use Disorder</td>
<td>Database of Opioid Users (Marketscan)</td>
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<td>Overdose</td>
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<tr>
<td>Diversion</td>
<td>RADARS (Drug Diversion)</td>
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<tr>
<td>Doctor Shopping</td>
<td>IMS Prescription Data</td>
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</tbody>
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Data adjusted for prescription volume

National Survey of Drug Use and Health, OxyContin Nonmedical Use

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

Oxycodone ER

Oxymorphone ER

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

Alternate Explanations Fail the Hill Temporality and Specificity Criteria

- **Oxycodone ER**
- **All Other Opioids**

- **PDMP Initiation**

- **Reformulation**
- **WA Rx Guidelines**
- **Natl Drug Take Back**
- **FL TIRF REMS**
- **ER/LA REMS**
- **HC-APAP Tramadol**
- **NY/ACEP Rx Guidelines**

Per 100,000 Population
What Will Capture Category 4?

March is one of the peculiarly dangerous months to speculate…

“The others are July, January, April, October, May, November, June, September, December, August and February.”
FDA Guidance on ADFs

• Demonstrate abuse-deterrent properties “meaningfully deter abuse, even if they do not fully prevent abuse”
  – Abuse: intentional, non-therapeutic use of a drug or substance, even once, to achieve a desirable psychological or physiological effect

• “Results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting”

• Add to the totality of evidence to support ADF claim
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.